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**PHD**

**Dynamic kinetic resolution of secondary alcohols and esters**

Dinh, Phi Manh

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# **Dynamic Kinetic Resolution of Secondary Alcohols and Esters**

**Submitted by Phi Manh Dinh  
for the degree of PhD  
of the University of Bath  
1999**

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Finally, my deepest gratitude goes to my family who have supported me and looked after me for so long. And I would like to dedicate this thesis to all the members of my family for everything they have done for me.

## Abbreviations

$\alpha$ -CT	$\alpha$ -Chymotrypsin
acac	Acetoacetate
AcOH	Acetic acid
ADHD	Attention deficit hyperactivity disorder
Al(O <sup><i>i</i></sup> Pr) <sub>3</sub>	Aluminium isopropoxide
Asp	Aspartate
Bemp	2- <i>tert</i> -Butylimino-2-diethyl-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine
Bemp-P	2- <i>tert</i> -Butylimino-2-diethyl-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine on polystyrene
Bipy	Bipyridine
CAL	<i>Candida antarctica</i> lipase
CCL	<i>Candida cylindracea</i> lipase
CdCl <sub>2</sub>	Cadmium chloride
CLEC	Cross-linked enzyme crystals
CLEC-17	Crossed-linked enzyme crystals (CRL)
CLEC-20	Crossed-linked enzyme crystals (PCL)
CoCl <sub>2</sub>	Cobalt chloride
cod	Cyclooctadiene
conv	Conversion
CRL	<i>Candida rugosa</i> lipase
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene

DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexyl carbodiimide
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DIPAT	Diisopropylaluminium trifluoroacetate
DKR	Dynamic kinetic resolution
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dppe	$(\text{C}_6\text{H}_5)_2\text{P}(\text{CH}_2)_2\text{P}(\text{C}_6\text{H}_5)_2$
DPPA	Diphenylphosphorylazide
E	Enantiomeric ratio
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee	Enantiomeric excess
eq	Equivalent
Et <sub>2</sub> O	Diethyl ether
Et <sub>3</sub> N	Triethylamine
EtOAc	Ethyl acetate
EtOH	Ethanol
FeCl <sub>2</sub>	Iron chloride
h	Hour(s)
H <sub>2</sub> SO <sub>4</sub>	Sulfuric acid
HCl	Hydrochloric acid
HCO <sub>2</sub> H	Formic acid

hd	Hexadiene
Hex	Hexane
HgSO <sub>4</sub>	Mercuric sulfate
His	Histidine
HLE	Horse liver esterase
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HSC	Hyflo super cell
IPA	Isopropyl alcohol
IR	Infra-red
KOH	Potassium hydroxide
La(O <sup><i>i</i></sup> Pr) <sub>3</sub>	Lanthanum isopropoxide
LDA	Lithium diisopropylamide
MeCN	Acetonitrile
MeOH	Methanol
MgCl <sub>2</sub>	Magnesium chloride
MgSO <sub>4</sub>	Magnesium sulfate
min	Minutes
MPV	Meerwein-Ponndorf-Verley
MPVO	Meerwein-Ponndorf-Verley-Oppenauer
MTBE	<i>tert</i> -Butyl methyl ether
NaBH <sub>4</sub>	Sodium borohydride
NaOH	Sodium hydroxide
NMR	Nuclear magnetic resonance

OAc	Acetate
Oct <sub>3</sub> N	Trioctylamine
<i>p</i> -TsOH	<i>Para</i> -Toluenesulfonic Acid
PCL	<i>Pseudomonas cepacia</i> lipase
PFL	<i>Pseudomonas fluorescens</i> lipase
PNB	<i>para</i> -Nitrobenzaldehyde
PPE	Polyphosphate ester
PPh <sub>3</sub>	Triphenylphosphine
PPL	Pig pancreas lipase
py	Pyridine
R <sub>f</sub>	Retention factor
R <sub>t</sub>	Retention time
RT	Room temperature
SAM-1	Lipase from <i>Pseudomonas fluorescens</i>
SBL	<i>Subtilisin bacillus lentus</i>
Ser	Serine
SmI <sub>2</sub>	Samarium diiodide
<i>t</i> -BuLi	Tertiary butyllithium
TBA	Tetrabutylammonium
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
UV	Ultra-violet
Yb(O <sup><i>i</i></sup> Pr) <sub>3</sub>	Ytterbium isopropoxide

## Abstract

The biotransformation of a racemic 1-phenylethan-1-ol (**25**) into the corresponding acetate using an enzyme has been successfully achieved. The maximum yield obtained from this reaction was 50% with >99% ee. *In situ* racemisation of the unreacted alcohol coupled with an enzymatic resolution reaction gave >50% conversion of enantiomerically enriched product, in >99% ee. Racemisations of secondary alcohols have been achieved using aluminium, rhodium, ruthenium and iridium catalysts. The racemisation process proceeds through a hydrogen transfer mechanism and the alcohol is temporarily oxidised into the corresponding ketone. A combined one-pot racemisation and enzymatic resolution reaction has been demonstrated to give (R)-1-acetoxy-1-phenylethane (R)-**26**, at 76-82% conversion with 80->99% ee.

The racemisation of esters using weak organic bases was studied. Selective racemisation of phenyl-(2-phenyl)propionate (S)-**97** was achieved under conditions containing DABCO. The racemisation procedure was applied to enzymatic hydrolysis of racemic (**97**) and preliminary results have shown 61-73% conversion in 19-65% ee of product (S)-2-phenyl propionic acid, (S)-**92**.

# **Chapter 1**

## A.1.0 Enzymatic Resolution Reactions

### A.1.1 Introduction

Enzymes are naturally occurring proteins and they are essential for the transformations of biochemical pathways in living things. Enzymes are catalysts that exist in both plants and animals and their roles are to carry out complex chemical reactions efficiently. They are in general very fastidious, highly specific, and very sensitive to temperature and pH change. There are groups of enzymes, however, that can tolerate high temperatures and strongly basic conditions. These are classified as thermophiles and alkaliphiles, respectively.

Enzyme-catalysed reactions work by lowering the activation energy of the reaction. They alter the rate of the reaction but they do not change the equilibrium, hence they are reversible. At the end of the reaction the catalysts themselves are unchanged and they can be reused. Enzymatic resolutions possess two expressions: *specific activity* and *turnover number*.<sup>1</sup>

#### 1. *Specific activity*

This is the specific activity of an enzyme with a given substrate. Catalytic activity is described as the amount of substrate ( $\mu\text{moles}$ ) reacted per minute per milligram of enzyme protein at a fixed temperature (usually 37 °C). For example,

$$[1.0 \mu\text{molemin}^{-1} (\text{mg. enzyme})^{-1} \equiv 1.0 \text{ Unit of activity}]$$

#### 2. *Turnover number*

This refers to the catalytic activity related to the number of active sites that are possessed by the enzyme obtained. When the molecular weight of an enzyme is



known, i.e. a pure enzyme sample, the turnover number is expressed in  $\mu\text{moles}$  substrate reacted per minute per  $\mu\text{mole}$  of enzyme.

$$[\text{Turnover number (units)} = \text{mole min}^{-1} (\text{mole enzyme})^{-1}]$$

For example, an enzyme has a specific activity of  $0.0015 \mu\text{mole min}^{-1} (\text{mg. enzyme})^{-1}$

<sup>1</sup>. The molecular weight of enzyme is 24,000, so 1.0 mg of enzyme protein is  $42 \times 10^{-9}$  mole or 42 nmoles of enzyme. Therefore,

$$\begin{aligned} 0.0015 \mu\text{mole min}^{-1} (\text{mg. enzyme})^{-1} &= 1.5 \text{ nmoles min}^{-1} (\text{mg. enzyme})^{-1} \\ &= 1.5 \text{ nmoles min}^{-1} (42 \text{ nmoles enzyme})^{-1} \end{aligned}$$

$$\text{Turnover number} = 0.036 \text{ mole min}^{-1} (\text{mole enzyme})^{-1}$$

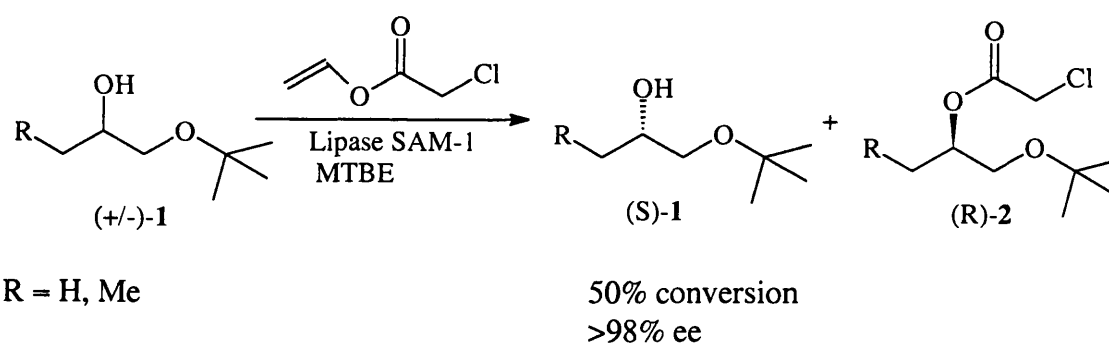
Enzymes are made up of three different types of protein structures. These are, primary, secondary and tertiary proteins which consist of L-amino acid residues linked by peptide bonds and hydrogen bonds cross-linking. Enzymes contain many chains of amino acids and the properties for selecting one substrate from a mixture depends on the shape of the active site. They can often be inhibited by compounds which are similar to the substrate. These compete to occupy the active site and prevent any biotransformation processes. This is known as competitive inhibition, where substrate and non-substrate having similar structures compete for the same active site. Competitive inhibition is reversible depending on the amounts of substrate available and the amounts of competitive-inhibitor present. Another type of inhibition is non-competitive inhibition which can be caused by heavy metals. Enzymes are deactivated or modified when metals bind onto the control site. These inhibitors prevent catalytic activities of enzymes and possibly change the shape of the substrate active site. Generally non-competitive inhibition is irreversible.

In recent years organic chemists have utilised enzymes for the synthesis of biologically active compounds. Although enzymatic resolution reactions are highly enantioselective, the maximum obtainable yield is only 50% and the remaining 50% of the starting material is normally discarded or recycled.

### A.1.2 Synthetic Applications

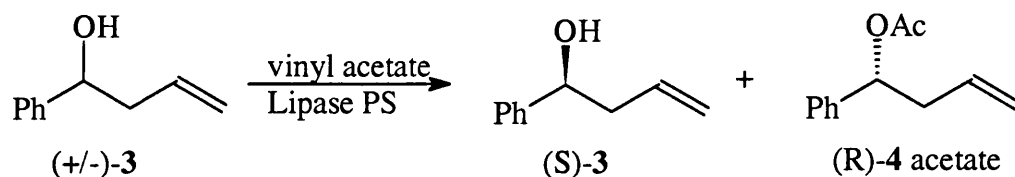
Enantiomerically pure drugs have played a vital part in the pharmaceutical industry. In the past many of the drug compounds were synthesised as a racemic mixture. We have learnt, however, that different enantiomers can induce different effects. Therefore enzymatic resolutions have been a popular choice for the preparation of enantiomerically pure compounds. The synthesis of enantiomerically pure oxiranes using enzymatic resolution has offered a short and facile route.<sup>2</sup> For example, enzyme-catalysed transesterification of racemic (**1**) gave chloroacetate (**(R)**-**2** with 50% conversion and >98% ee (**Scheme 1**).

**Scheme 1**



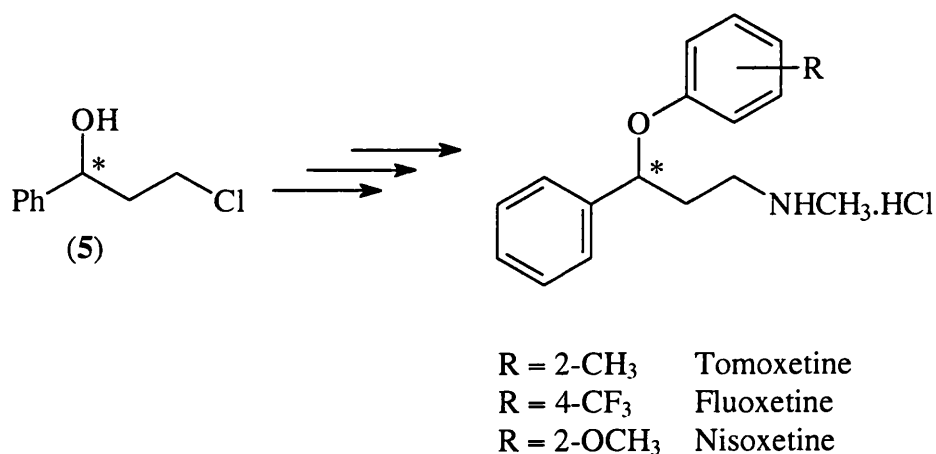
*Pseudomonas cepacia* (Amano PS) catalysed acylation of racemic 1-phenyl-3-buten-1-ol (**3**) under non-aqueous conditions (**Scheme 2**) to give 98% ee of (**R**)-**4** acetate in >47% isolated yield and the remaining alcohol (**S**)-**3** was recovered in 91% ee.<sup>3</sup>

## Scheme 2



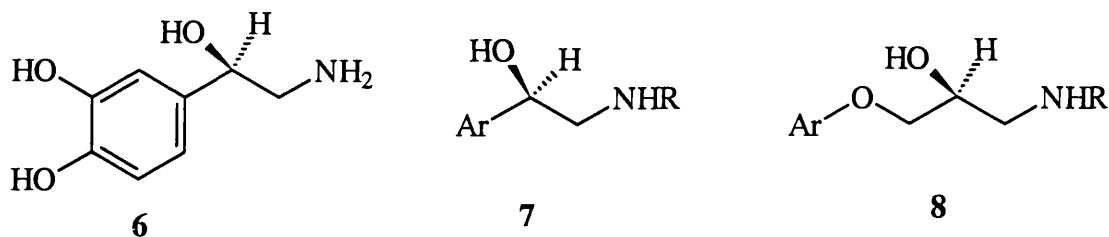
The enantiomerically pure (S)-3 obtained was a convenient starting material for the manufacture of (S)-Fluoxetine. The production of both the (R)- and (S)-3-chloro-1-phenyl-1-propanol (**5**) by enzymatic resolution reaction has also been reported<sup>4</sup> as an efficient route to the preparation of enantiomerically pure antidepressants: Tomoxetine, Nisoxetine and Fluoxetine (**Scheme 3**). The synthesis of enantiomerically pure Fluoxetine and related compounds is of interest for the treatment of depression, anxiety, alcoholism, obesity, chronic pain and bulimia.<sup>5</sup>

## Scheme 3



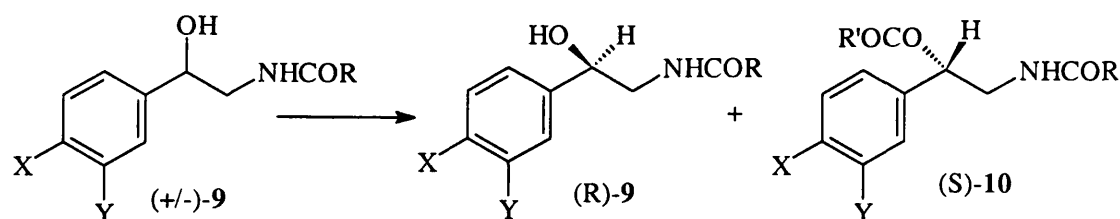
Adrenergic drugs are an important class of  $\beta$ -blockers which are being used to treat high blood pressure and heart disease. The preparation of (R)-noradrenaline (**6**) and many adrenergic drug derivatives such as 2-amino-1-arylethanol (**7**) and 1-amino-3-aryloxy-2-propanol (**8**) (**Scheme 4**) have been achieved using enzyme-catalysed acylation reactions.<sup>6</sup>

#### Scheme 4



*Pseudomonas cepacia* lipase (lipase PS from Amano pharmaceuticals) catalysed acylation of racemic alcohol (**9**) with propionic anhydride in toluene/THF (3:1) at 47°C to give (R)-**9** in 99% ee and (S)-**10** in 98% ee at 50% conversion (**Scheme 5**). Since sterically hindered secondary alcohols are slow reacting, acyl donors which are most effective were used. Acid anhydrides were found to be the most reactive acyl donors, however acids were liberated during the reaction. Therefore the pH must be carefully monitored.

#### Scheme 5

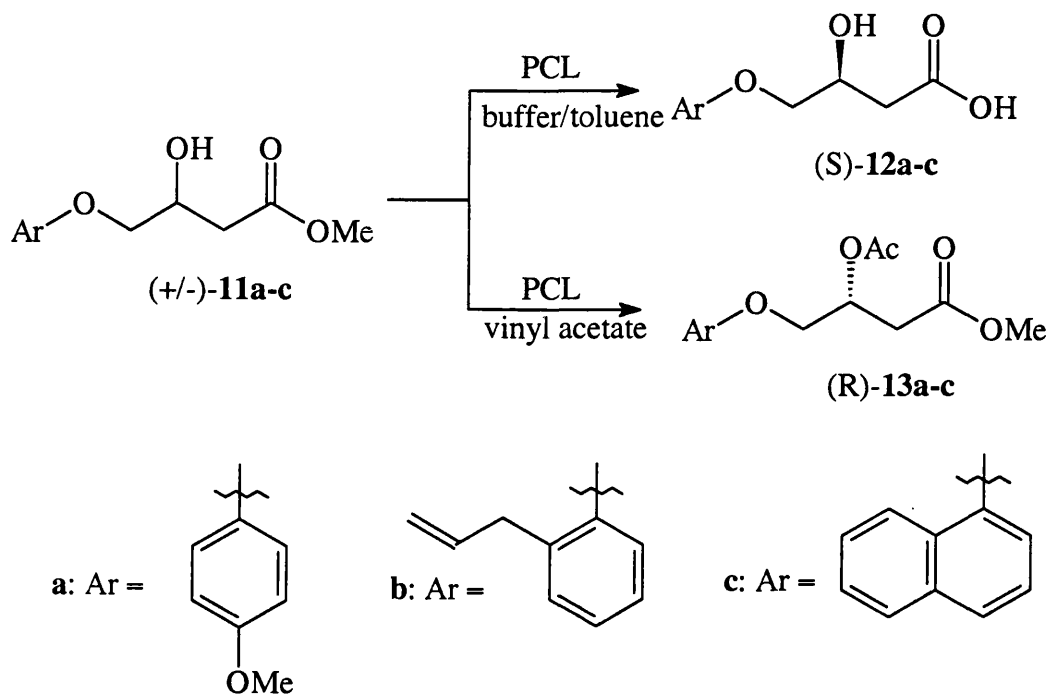


X = Me after 6 hours  
X = OMe after 24 hours

Y = H, OR

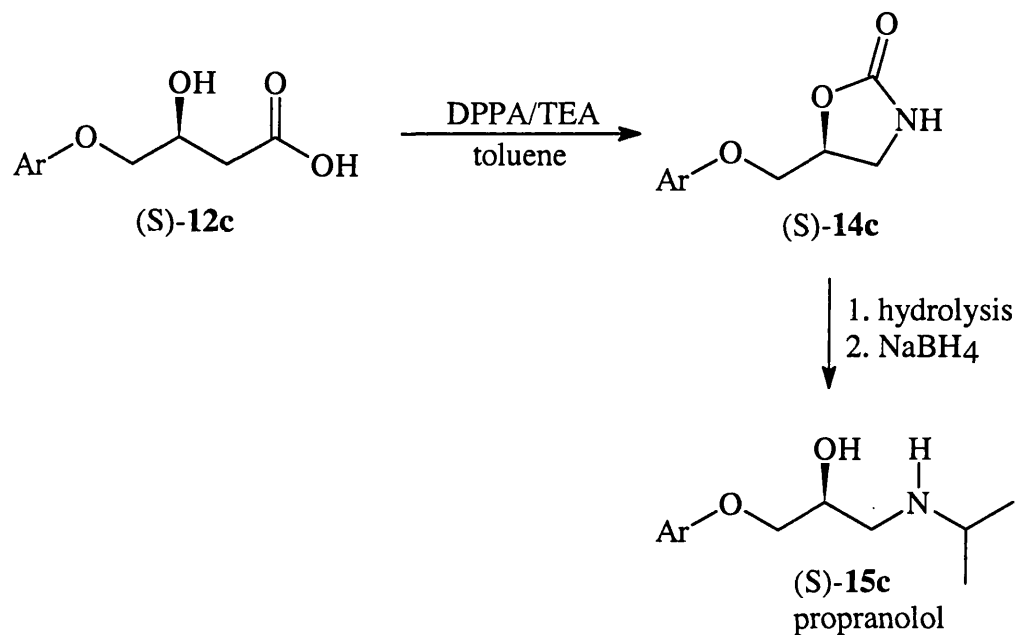
The resolution of 3-hydroxy methyl ester (**11a-c**)<sup>7</sup> either by lipase-catalysed hydrolysis in aqueous buffer/toluene or acylation with vinyl acetate in hexane using PCL gave >98% ee in all cases at around 50% conversion (**Scheme 6**).

## Scheme 6



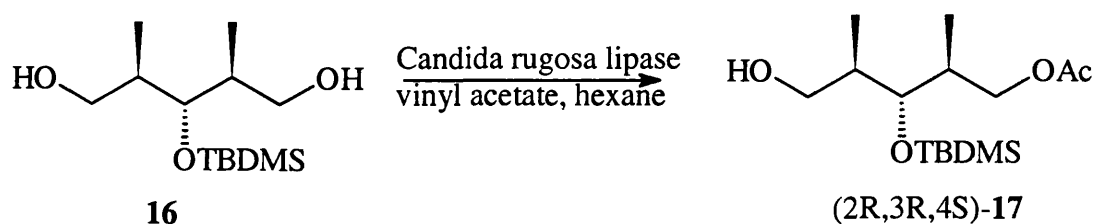
Subsequent reaction of pure acid (S)-12c obtained with diphenylphosphorylazide (DPPA) and triethylamine (TEA) in toluene gave oxazolidinone (S)-14c in 81% yield. (S)-14c was then hydrolysed and reduced using sodium borohydride (NaBH<sub>4</sub>) to give (-)-(S)-propranolol (15c) (Scheme 7). The preparation of (S)-15c and enalapril (angiotensin converting enzyme inhibitor) by other enzymatic routes were also reported.<sup>8</sup>

## Scheme 7



Enzymatic desymmetrization of meso-2,4-dimethyl-1,3,5-pentanetriol derivative (**16**) was successfully catalysed by lipase from *Candida rugosa* and vinyl acetate to afford 94% isolated yield of the corresponding mono ester (2R,3R,4S)-**17** with 97% ee ( $[\alpha]_D^{22} = -8.6$  (c 2.37,  $\text{CHCl}_3$ )) (Scheme 8). Compound (2R,3R,4S)-**17** is an important fragment which is found in many natural products such as rifamycin, calyculin A, swinholide A, muamvatin and aplyronine A.<sup>9</sup>

## Scheme 8

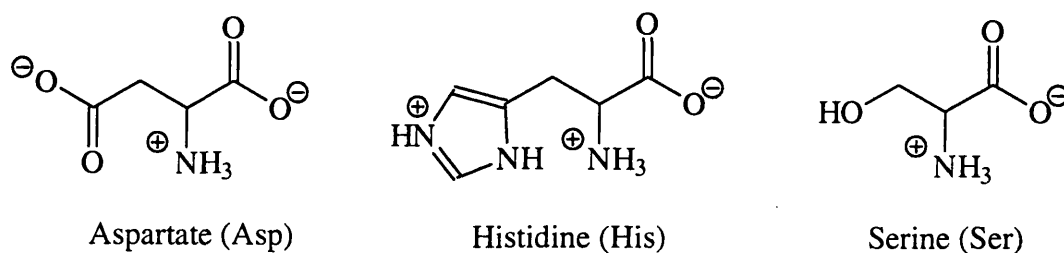


Enzymatic resolution has led to facile synthesis of some insect pheromones such as pheromones of *Crematogaster* ants.<sup>10a-b</sup> Kinetic resolution reactions have become a useful tool for the resolution of many natural product precursors. Enzymes have also been used for the preparation of catalysts,<sup>11</sup> enantiomerically pure substituted cyclohexanols<sup>12</sup> and resolution of mucolytic drug ( $\pm$ )-*trans*-sorbiterol.<sup>13</sup>

### A.1.3 Enzyme-Catalysed Transesterification Reactions

Hydrolases are groups of enzymes that catalyse the hydrolytic cleavage of bonds. Enzymes of this class are readily available e.g. proteases, amylases, acylases, lipases and esterases. There are about 30 different lipases that are commercially available. Many lipase enzymes are assumed to contain a triad of Ser...His...Asp.<sup>1,14</sup> residue in their active site (**Scheme 9**).

**Scheme 9**

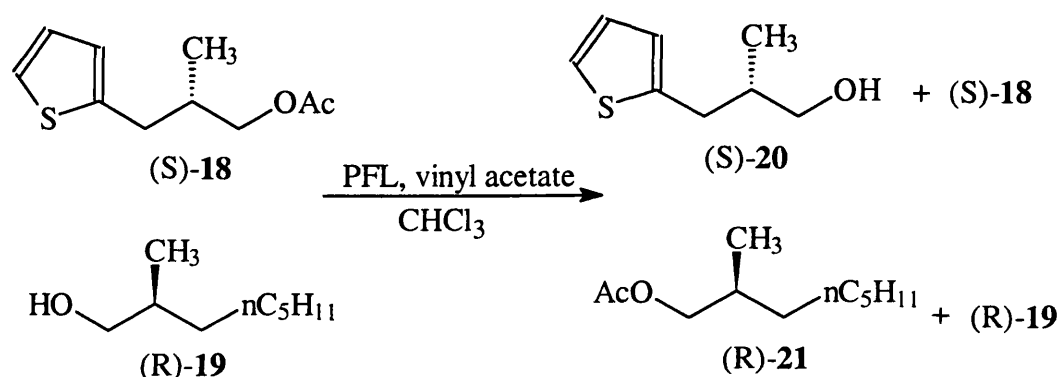


Enzyme-catalysed acylation reactions require a suitable acyl donor. Vinyl acetate is the simplest acyl donor and it is readily available. Ideally, an irreversible, enantioselective enzymatic resolution of a racemic starting material will give 100% ee product and 100% ee of the remaining substrate. At higher than 50% conversion the substrate is practically enantiomerically pure and this depends on the enantiomeric ratio (E)<sup>15a-b</sup> between the fast and the slow reacting enantiomers. In contrast, reversible reactions will give low enantiomeric purity of the remaining

substrate, even at high E-values. In reversible reactions, the enantiomeric excess of the starting material should reach a maximum at greater than 50% conversion and then decrease to zero when the conversion becomes equilibrated. To achieve an irreversible kinetic resolution, acyl donors such as vinyl esters<sup>16</sup> are essential. The by-products of these rapidly tautomerise to the aldehydes or ketones. Since these enols are electrophilic species, they are unable to react with the acyl-enzyme intermediate and thus, they can be easily removed by evaporation depending on the boiling point. Vinyl esters are not reversible acyl donors but the generated acetate product<sup>17</sup> can cause a reaction to be reversed.

Höberg and co-workers<sup>18</sup> have investigated the reversibility of enzyme-catalysed acylation reactions. The reaction conditions were designed to mimic >50% acylation of the racemic 2-methyl-3-(2-thienyl)propanol (**20**) by using one equivalent of ester (S)-**18** (the fast reacting enantiomer) and one equivalent of the alcohol (R)-**19** (a mimic of the slow reacting enantiomer) (**Scheme 10**). It was shown that (S)-**18** was hydrolysed to give (S)-**20** when the reaction was ran under conditions containing PFL in vinyl acetate (4 eq). Clearly acetate (S)-**18** was acting as an acyl donating agent in this reaction.

**Scheme 10**

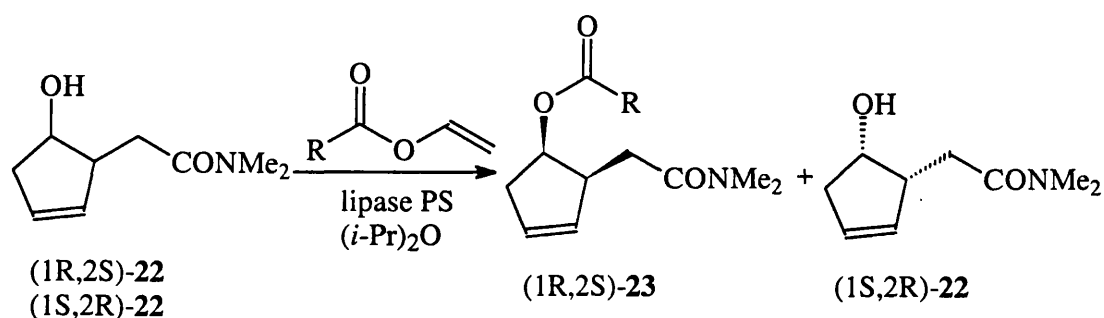




#### A.1.4 Effect of Acyl Donors

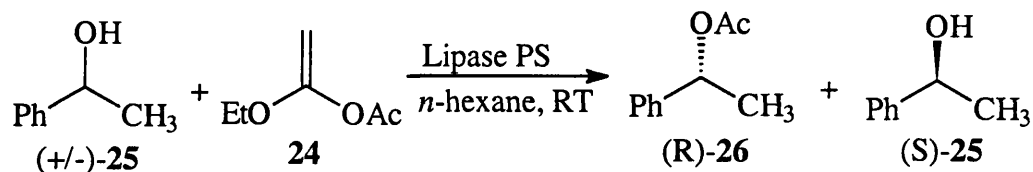
Utaka and co-workers<sup>19</sup> have investigated the transesterification of 2-[(N,N-dimethylcarbamoyl)-methyl]-3-cyclopenten-1-ol (**22**) with different vinyl esters (**Scheme 11**).

**Scheme 11**



The enantioselectivity was enhanced from changing vinyl acetate to vinyl butyrate<sup>20</sup> and suppressed when longer chain lengths were used. Vinyl chloroacetate gave fast reaction rate with good enantioselectivity. Vinyl trifluoroacetate, however, displayed poor reactivity and selectivity. The acylation rate of vinyl butyrate was slower than vinyl acetate, but when acyl donors longer than that of vinyl butyrate were used, the rate of reaction was increased. Kita *et al*<sup>21</sup> have also reported 1-ethoxyvinyl acetate (**24**) as a novel, highly selective, and a fast-reacting acyl donor. The synthesis of (**24**) was conducted using ruthenium-catalysed addition of acetic acid to ethoxyacetylene.<sup>22</sup> Conventional vinyl acetate gave reactive acetaldehyde by-products resulting in enzyme deactivation.<sup>23</sup> Enzymatic resolution of 1-phenyl ethanol (**25**) using 1-ethoxyvinyl acetate released only volatile ethyl acetate as a single by-product.<sup>24</sup> The acylation reaction of racemic alcohol (**25**) using lipase SP (*Pseudomonas* sp. from Amano) and acyl donor (**24**) went to 50% conversion after 3 hours to give the acetate product (R)-**26** in >95% ee (**Scheme 12**).

## Scheme 12



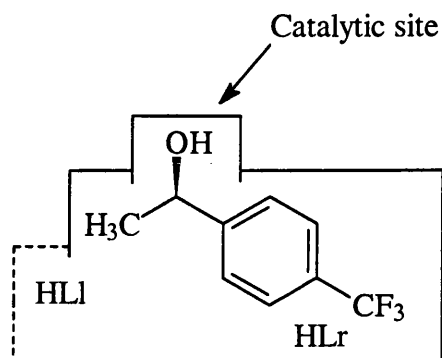
Anthonsen *et al*<sup>25</sup> have reported studies on enzyme-catalysed transesterification of secondary alcohols with 2-chloroethyl butanoate, 2,2,2-trichloroethyl butanoate, vinyl butanoate and butanoic anhydride. Although 2-chloroethyl butanoate was a good acyl donating agent and gave a very high E-value, the reaction was reversible.

Acyl donating agents mediated inversion of enantioselectivity was also documented.<sup>26</sup> For example, the resolution of mandelic acids using lipase from *Pseudomonas sp.* and vinyl acetate gave the (S)-acetate product. When the reaction was repeated with vinyl chloroacetate the (R)-product was obtained.

### A.1.5 Predictive Active Site Models for Lipase Enzymes

A predictive model for lipase YS (from *Pseudomonas fluorescens*) has been reported.<sup>27</sup> Lipase YS preferentially acylated primary alcohols having a hydroxymethyl moiety with an (S)-configuration and secondary alcohols with an (R)-configuration to give the corresponding acetates, using isopropenyl acetate in diisopropyl ether. The development of active site models for enzymes was attempted to give an accurate prediction of the faster-reacting enantiomer. Based on the enantioselectivity observed with different substituents<sup>28</sup> at the chiral centre of the substrate, the right hydrophobic binding site (HLr) was found to be larger than the left hydrophobic binding site (HLl) as shown (Scheme 13). Compounds possessing a

phenyl moiety with polar groups or electronegative atoms at the *para*-position were shown to have a high E-value. Therefore the HLr pocket is polar in character and polar groups are more favourable in being accommodated in this region.



**Scheme 13.** Representation of a top perspective view of the active site model.

Burgess and Jennings have also reported<sup>29</sup> an active site model for lipase AK (from *Pseudomonas sp.*) They have concluded that the poor fitting of substrates at the enzyme active site represent the slower reacting enantiomer whereas the faster reacting enantiomer displayed good fitting at the enzyme active site. The prediction of active site models for lipase QL (from *Alcaligenes sp.*)<sup>30</sup> and porcine pancreatic lipase (PPL)<sup>31</sup> also gave similar results.

#### A.1.6 The Influence of Solvent

Enzymatic resolution reactions have been formally operated under aqueous reaction conditions. Many organic compounds, however, do not dissolve in aqueous solvents. Therefore enzymatic resolution reactions working in organic solvents are highly desired, but only a certain class of enzymes can operate in organic solvents.<sup>32a-b</sup> In general enzymatic acylation reactions of racemic alcohols have shown high catalytic activity in organic solvents.<sup>1</sup> The resolution of phenyl-1,2-diol using lipase from

*Pseudomonas cepacia* (Amano PS) in solvents such as acetone, dichloromethane and 1,4-dioxane gave longer reaction times than in diethyl ether, t-butyl methyl ether, 1,1,2-trichloro-1,2,2-trifluoroethane or a mixture of THF/toluene (1:4).<sup>33</sup> Lipase enzymes are more thermally stable in anhydrous organic solvents than in aqueous solvents. The stabilisation of enzymes in organic solvents may be due to the increased adsorption, cross-linking, or covalent binding to the hydrophilic surface of the protein. Commercially available crude lipase enzymes, however, contain up to 7.0% water. Drying the crude enzymes under vacuum can reduce the amount of water present. Acylation reactions require acyl donors and some of these acyl donating agents can also serve as solvents. A typical example is vinyl acetate. Most often the enantioselectivity of enzyme-catalysed acylation reactions of alcohols in organic solvents are higher than the hydrolysis of the corresponding acetate in water.<sup>19,20,34</sup>

## **B.1.0 Oxidation and Reduction Reactions**

### **B.1.1 Introduction**

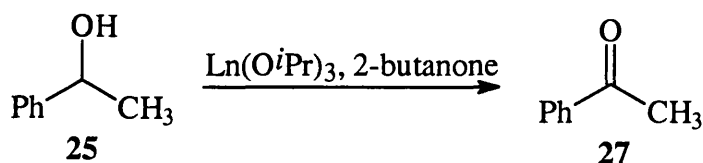
Many metals in the transition period have variable oxidation states and these properties of such have made them very useful for the oxidation and reduction of many compounds.<sup>35</sup> The other group of metal catalysts belong to the lanthanide series and according to Imamoto,<sup>36</sup> the toxicity of lanthanide salts such as chlorides, nitrates and citrates have almost the same level of toxicity as group one salts. Compared with the transition metal catalysts the lanthanides are relatively safe to use. Aluminium is not classed as a transition metal, but aluminium alkoxides have been well established<sup>37</sup> for the Meerwein-Ponndorf-Verley (MPV) reduction<sup>38</sup> of aldehydes and ketones and the Oppenauer oxidation<sup>39</sup> of alcohols. Amongst the commonly known hydrogenating catalysts, nickel,<sup>40a-d</sup> zirconium<sup>41a-b</sup> and platinum/ML (M = Sb,

Sr)<sup>42</sup> have also been cited to catalyse the transfer hydrogenation reactions of ketones and aldehydes.

### B.1.2 Samarium Catalysts

The lanthanide metal alkoxides have been effectively used to promote the MPV reduction and Oppenauer oxidation reactions. The range of lanthanide alkoxides<sup>43a-b</sup> can be generated from the easily prepared lanthanide halides.<sup>44</sup> Although samarium(II) iodide (SmI<sub>2</sub>) is only a salt, it has been shown to reduce many aldehydes and ketones when using a stoichiometric amount. The reduction of acetophenone (**27**) by SmI<sub>2</sub> in the presence of methanol was successful at ambient temperature and after 24 hours the corresponding alcohol (**25**) was obtained in 80% yield. Lanthanide alkoxides, however, are more efficient for the Meerwein-Pondorf-Verley-Oppenauer (MPVO) reactions. The Oppenauer oxidation of alcohol (**25**) into ketone (**27**) proceeded quantitatively using Yb(O<sup>*i*</sup>Pr)<sub>3</sub> (0.05 eq) and 2-butanone (16 eq) at 80 °C (Scheme 14). The presence of water can cause deactivation of the metal alkoxides and this was controlled with molecular sieves 4Å and the yields were improved.

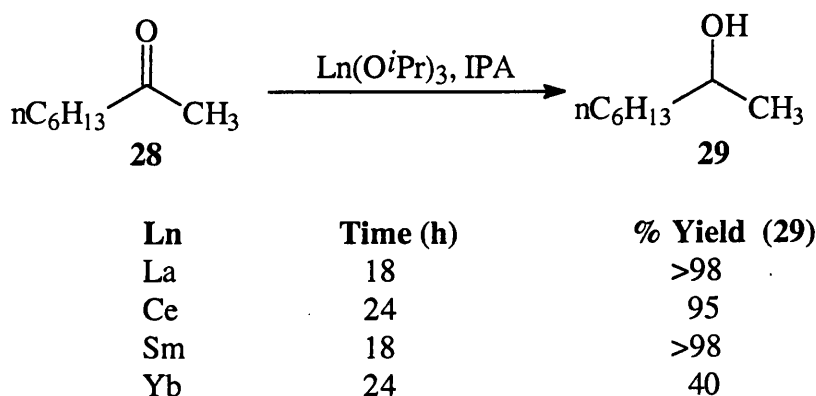
**Scheme 14**



Ln	Time (h)	% Yield ( <b>27</b> )
La	60	75
Ce	48	15
Sm	24	70
Yb	24	98

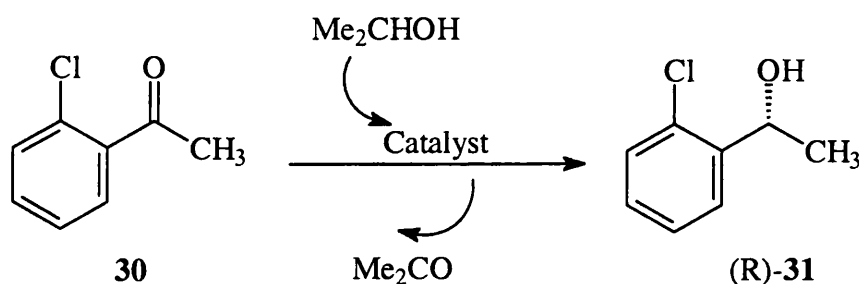
In contrast to the above reactions the MPV reduction of 2-octanone was achieved with >98% yield using  $\text{La}(\text{O}^i\text{Pr})_3$  in 2-propanol at 80 °C (**Scheme 15**) and molecular sieves were not required.

**Scheme 15**



The main interest of lanthanide catalysts was directed toward enantioselective reduction of ketones.<sup>45a-c</sup> Samarium (III) complexes generated from freshly prepared  $\text{SmI}_2$  and chiral bi- and tridentate ligands were screened for the asymmetric reduction of *o*-chloroacetophenone (**30**)<sup>43b</sup> using IPA (25 eq) at 25 °C (**Scheme 16**).

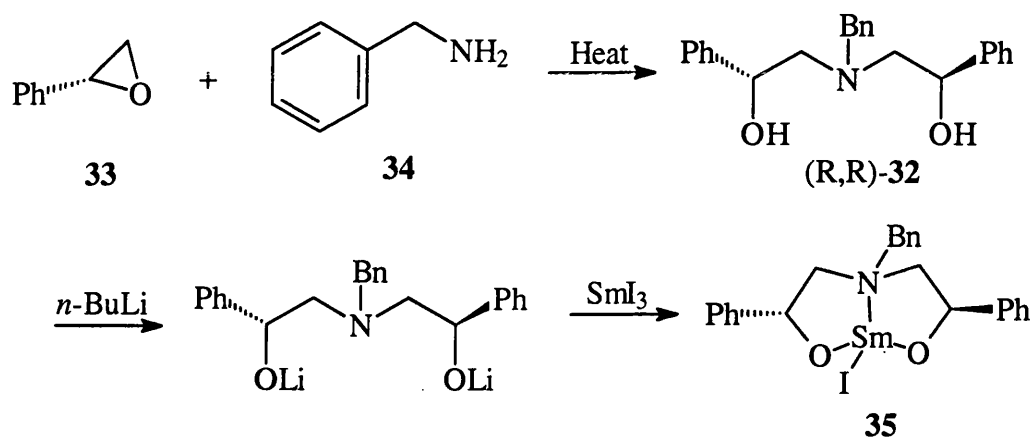
**Scheme 16**



Enantiomerically pure (R,R)-**32** designed by Evans *et al*<sup>46</sup> gave excellent enantioselectivities and reactivities for the reduction of alkyl and aryl ketones. The preparation of (R,R)-**32** was simply by heating (R)-styrene oxide (**33**) and benzylamine (**34**) together at 100 °C. This was followed by double deprotonation

using *n*-BuLi and subsequent complexation with SmI<sub>3</sub> in THF to give (35) (Scheme 17).

**Scheme 17**



The reduction of ketone (30) using samarium catalyst (35) gave the corresponding alcohol (R)-31 in 97% ee at 100% conversion at ambient temperature over a 1-2 hours period. Lanthanide(III) complexes derived from NdI<sub>3</sub>, SmI<sub>3</sub>, and TbI<sub>3</sub> with ligand (R,R)-32 showed excellent selectivities and reaction times between 1.5-3.0 hours were observed.

### B.1.3 Aluminium Catalysts

MPVO reactions are commonly catalysed by aluminium alkoxides. Aluminium alkoxides transfer hydride reversibly to a carbonyl acceptor. Doering *et al*<sup>38</sup> have reported the use of sodium alkoxide and aluminium alkoxide catalysed oxidation-reduction reaction of carbonyl-carbinol systems.

A hydrogen donor is essential for the MPV reduction reactions. Hydrogen donors are mainly low molecular weight primary and secondary alcohols. The most commonly used is IPA because acetone is formed as a volatile side product and can easily be

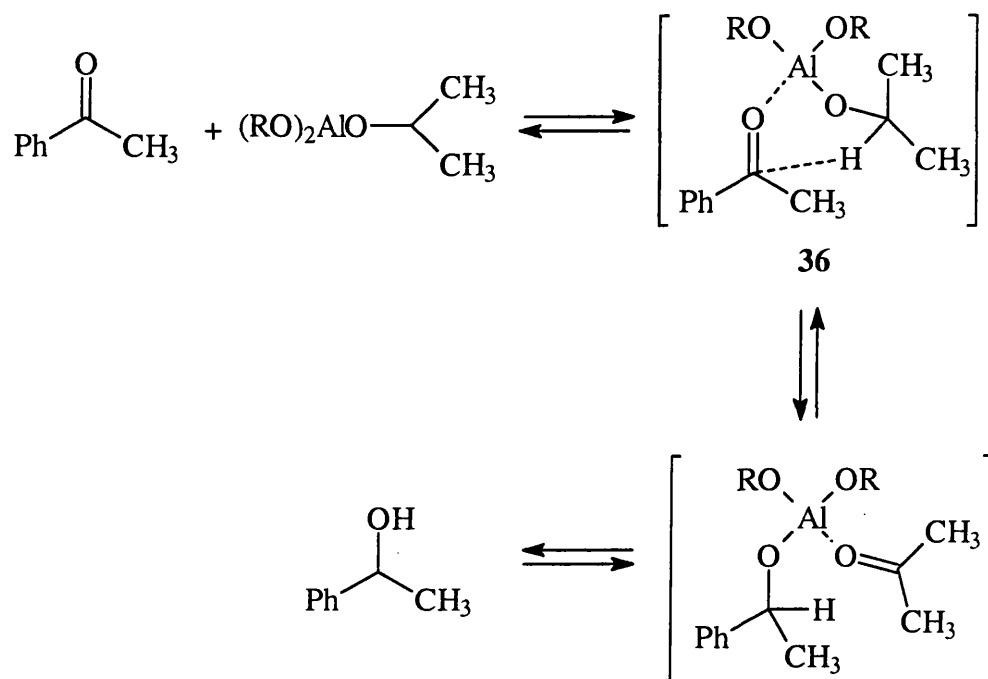
removed. Oppenauer oxidation reactions using aluminium *t*-butoxide have been exploited extensively for the synthesis of natural products.<sup>39</sup> The oxidation of an alcohol to a ketone required acetone as a hydride acceptor since acetone was the most feasible and versatile to use.

The reaction conditions, such as time and temperature, can be varied depending on the nature of the substrates and the oxidation/reduction potentials of the hydrogen acceptor and the hydrogen donor, respectively. Labile substrates can be oxidised at room temperature for several days and heat stable compounds can be heated at reflux or heated in a sealed tube for only a few hours.

The mechanism for aluminium catalysed MPVO redox reaction goes through a transition state (**36**) (**Scheme 18**). The balance of the equilibrium depends on the concentrations of the hydride donor and the hydride acceptor. To achieve a high conversion for the reduction reaction excess amount of the hydride donor (e.g. IPA) must be used.



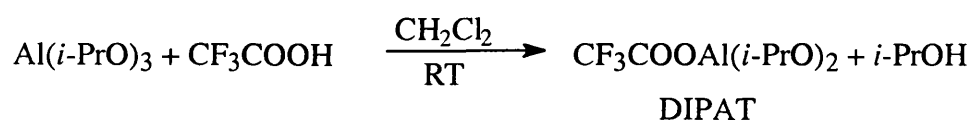
**Scheme 18**



The rates of aluminium alkoxide catalysed intramolecular MPVO reactions have been studied<sup>47</sup> with different alkali metal salts. Few reports, however, were found for catalytic<sup>43b</sup> and asymmetric<sup>48</sup> activities of aluminium alkoxides.

New metal alkoxides such as diisopropoxyaluminium trifluoroacetate (DIPAT) was documented<sup>49</sup> and DIPAT was synthesised by reacting aluminium isopropoxide with trifluoroacetic acid in dichloromethane at room temperature (**Scheme 19**). DIPAT was obtained as a white solid and is stable when stored under anhydrous conditions.

**Scheme 19**

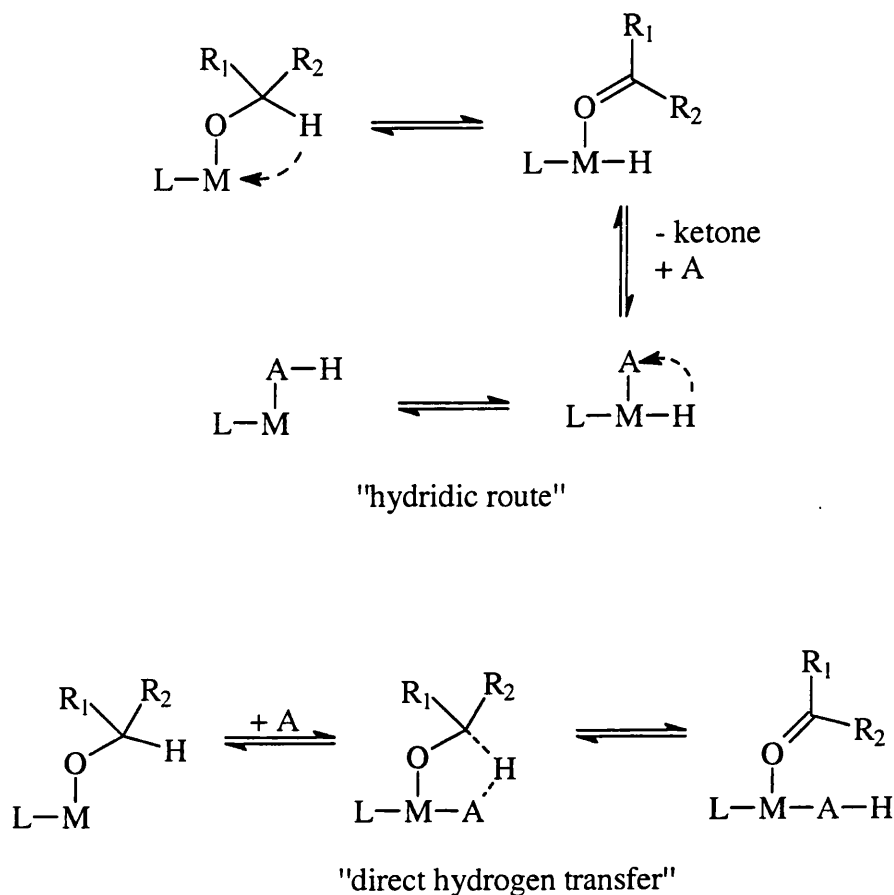


DIPAT was used for the reduction of various aldehydes and ketones at room temperature and the reduction of benzaldehyde into the corresponding alcohol was accomplished within 15 minutes employing 1 equivalent of the catalyst. The reduction of other aromatic aldehydes and ketones were comparatively slower. Accelerated Oppenauer oxidation<sup>50</sup> of secondary alcohols to the corresponding ketones was successfully achieved using DIPAT and *p*-nitrobenzaldehyde (PNB). Irrespective of the substrates, most alcohols were oxidised within 15-30 minutes at room temperature in benzene with stoichiometric requirement of DIPAT and PNB.

#### B.1.4 Rhodium Catalysts

The role of rhodium in asymmetric transfer hydrogenation has been extensively investigated.<sup>51</sup> Asymmetric hydrogen transfer reactions require a rhodium pre-catalyst and a chiral ligand. Rhodium pre-catalysts can be readily obtained and these can be  $[\text{Rh}(\text{cod})\text{Cl}]_2$ ,  $[\text{Rh}(\text{coe})_2\text{Cl}]_2$ ,  $\text{Rh}_2(\text{OAc})_4 \cdot 2\text{H}_2\text{O}$ , and  $[\text{Rh}(\text{hd})\text{Cl}]_2$  (cod = 1,5-cyclooctadiene, OAc = acetate, hd = 1,5-hexadiene, coe = cyclooctene). In hydrogen transfer reactions primary and secondary alcohols or formic acids provide a source of hydrogen. The advantages for using hydrogen donors over molecular hydrogen are avoidance of the risks associated with combustion and pressure constraints. Mechanistically there are two possible paths for the hydrogen transfer reactions (Scheme 20), “hydridic route” (hydride is inserted onto the metal) and “direct hydrogen transfer” (direct transfer of hydride from donor to acceptor, similar to MPVO type reactions).

**Scheme 20**



L = chiral or achiral ligand

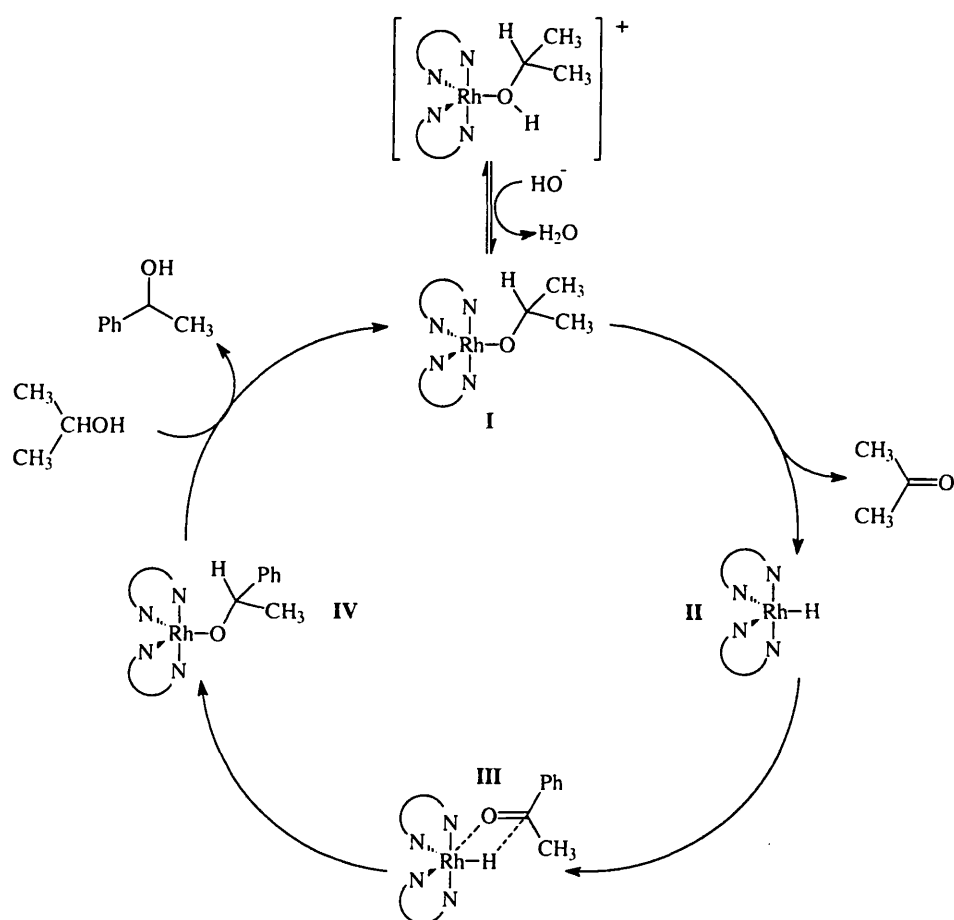
A = substrate having a prochiral centre

The transfer hydrogenation of ketones requires a strong base like potassium hydroxide or sodium hydroxide. The importance of a strong base relates to the deprotonation of IPA in the catalytic cycle which will then form the metal hydride  $[\text{M}(\text{L}-\text{L})\text{H}]$  species. Without the addition of alkoxide or hydroxide, no hydrogenation of ketone was observed and no conversion was also observed when triethylamine was used.<sup>52</sup> The rate of reaction was enhanced in the presence of a strong base and no reaction occurred if the concentration of the base was too low. Decomposition of the catalyst to inactive metallic rhodium was observed when the ratio of KOH : Rh was less than 3:1. Another advantage of using a strong base is to achieve a high catalytic

activity, thus allowing the reaction to operate at substrate to metal catalyst ratio as high as 1000:1.

Zassinovich and Mestroni<sup>53</sup> have suggested a catalytic cycle (**Scheme 21**) for the transfer hydrogenation of ketones using rhodium complexes with nitrogen ligands. The key step was the hydride insertion into the metal to form a rhodium hydride species **II**. This was followed by a hydride abstraction by the ketone (complex **III**) and subsequent formation of metal alkoxide **IV**. The catalytic cycle repeats with the displacement of the metal alkoxide **IV** by another alcohol.

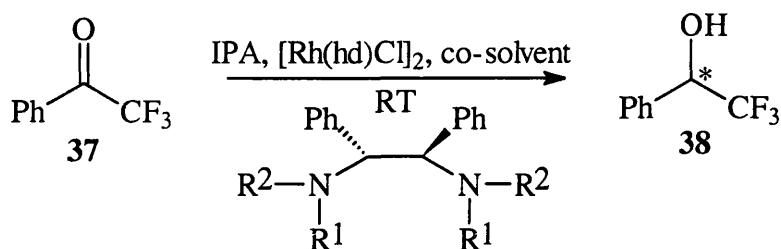
**Scheme 21**



The bulk of the transfer hydrogenation work was concentrated on the screening of many chiral ligands for the asymmetric reduction of ketones. Chiral phosphinooxazoline ligands<sup>54a-b</sup> gave good enantioselectivity for the catalytic asymmetric hydrosilylation<sup>55</sup> of ketones using rhodium(I) complexes. The asymmetric transfer hydrogenation of ketones using phosphine,<sup>56a-b</sup> diamines,<sup>57a-c</sup> Schiff bases<sup>58a-b</sup> bipyridine<sup>59</sup> and phenanthroline<sup>53,60a-b</sup> ligands were also documented. The use of ligands is essential. When not enough ligand was used decomposition of the metal catalyst was observed and in the absence of ligand the pre-catalyst employed was almost devoid of any catalytic activity. The concentration of ligands was thoroughly examined by Mestroni *et al*<sup>53</sup> for the transfer hydrogenation of ketones using phenanthroline. An optimum [ligand]/[catalyst] ratio of 4:1 was attained. This ratio, however, may vary depending on the choice of ligand used. The transfer hydrogenation reactions catalysed by cationic rhodium(I) complexes were also reported.<sup>61a-b</sup> In particular  $[\text{Rh}(\text{cod})(\text{dppe})]^+$  ( $\text{dppe} = (\text{C}_6\text{H}_5)_2\text{P}(\text{CH}_2)_2\text{P}(\text{C}_6\text{H}_5)_2$ ) was found to be most active for the reduction of cyclohexanone using IPA and a catalytic amount of KOH to give the corresponding alcohol in 99% conversion after 30 minutes.

The activity of rhodium catalyst was studied in different solvents. When the reduction of  $\alpha,\alpha,\alpha$ -trifluoroacetophenone (**37**)<sup>57a</sup> was conducted in a polar non-protic solvent (**Scheme 22**) the activity of the catalytic system was increased by 5-fold but the enantiomeric excess was decreased. The decrease in enantioselectivity was due to competitive co-ordinating abilities between the chiral ligand and the co-solvent used, especially in the cases of THF and acetonitrile. The addition of water decreased the rate of reaction but the enantiomeric excess was increased.

**Scheme 22**



$\text{R}^1, \text{R}^2 = \text{H, Me}$

Co-solvent	Time (days)	Conversion	% ee*
None	5	89	33
heptane	5	100	13
THF	1	100	15
water	8	95	41

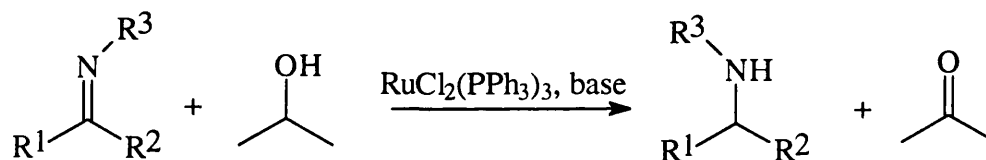
Experimentally the order in which the reagents are added is important and reactions are normally carried out under an inert atmosphere. Frequently IPA and acetophenone were distilled before use. The pre-catalysts were activated by refluxing in IPA for about 15 minutes in the presence of a ligand, followed with the addition of aqueous KOH solution. The reaction mixture was left under reflux for 1 hour and then stirred overnight at room temperature before addition of the substrate ketone. The catalyst solution usually changed to a dark coloration after refluxing.

### B.1.5 Ruthenium Catalysts

Ruthenium complexes<sup>51</sup> have been some of the most useful catalysts in organic chemistry. Ruthenium catalysts have strikingly similar properties to rhodium catalysts and they are very active even at room temperature. Ruthenium-catalysed Oppenauer type oxidation has been efficiently deployed in the synthesis of steroidal drugs.<sup>62</sup> The hydrogenation of ketones and aldehydes using chiral ruthenium(II)

catalysts and molecular hydrogen has been successfully achieved in high enantiomeric purity.<sup>63a-b</sup> It was also reported<sup>64</sup> that ketones and aldehydes were selectively reduced in the presence of olefinic or acetylenic groups under conditions containing  $\text{RuCl}_2[\text{P}(\text{C}_6\text{H}_5)_3]_3\text{-H}_2\text{N}(\text{CH}_2)_2\text{NH}_2\text{-KOH}$  system. In recent years the reduction of imines to amines *via* transfer hydrogenation pathway has been documented.<sup>65</sup> The reduction of imines was catalysed by  $\text{RuCl}_2(\text{PPh}_3)_3$  (0.5 mol%) and  $\text{K}_2\text{CO}_3$  (5 mol%) in refluxing IPA (**Scheme 23**). Low reaction rate was observed when NaOH was used in place of  $\text{K}_2\text{CO}_3$  and it is important that the IPA employed is dry since water reacts reversibly with imine affording amine and an aldehyde or a ketone. The generated aldehyde could deactivate the catalyst by reacting with the ruthenium catalyst to give carbonyl or hydridocarbonyl complexes.

**Scheme 23**



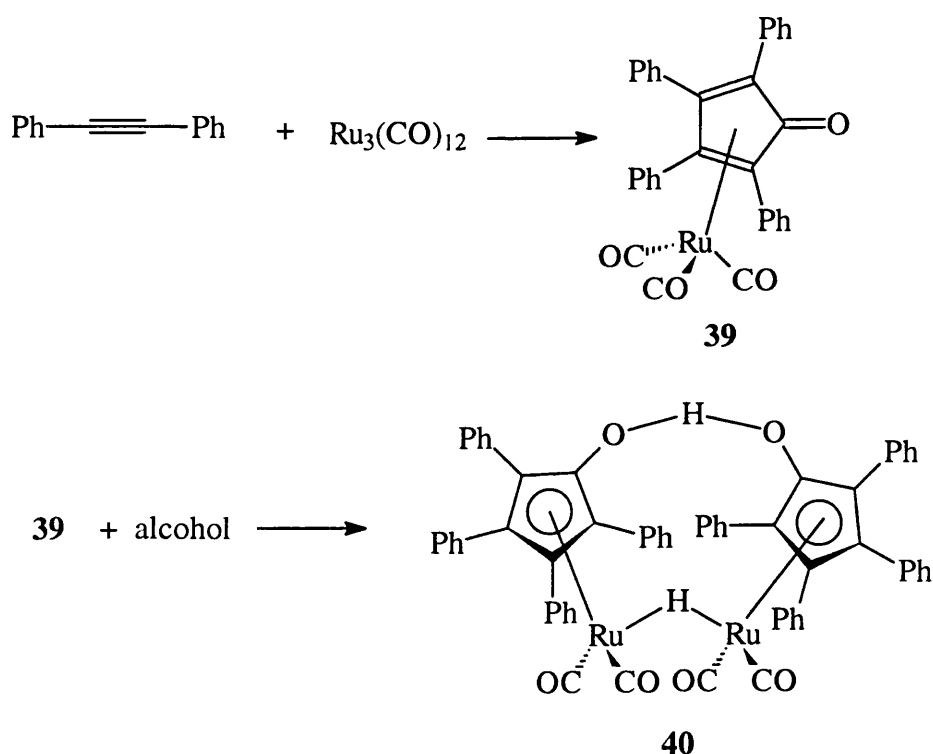
The oxidation of secondary alcohols under mild reaction conditions by acetone in the presence of a catalytic amount of  $\text{RuCl}_2(\text{PPh}_3)_3$ ,<sup>66</sup> and  $\text{RuCl}_2(p\text{-cymene})_2$ -catalysed oxidation<sup>67</sup> of non-activated alcohols by  $\text{MnO}_2$  were successfully achieved.

Many of the enantioselective transfer hydrogenations of ketones using ruthenium catalysts were actively pursued by Noyori,<sup>68a-c</sup> Knochel,<sup>69</sup> Helmchen,<sup>70</sup> and their co-workers. The kinetic resolution of racemic unsaturated secondary alcohols by chiral ruthenium-catalysed hydrogen transfer was also successfully accomplished by Noyori

*et al.*<sup>71</sup> Bäckvall *et al.*,<sup>72a-b</sup> however, were more interested in the rate studies<sup>73</sup> than the asymmetric transfer hydrogenation reactions.

It was Shvo and Menashe<sup>74a-b</sup> who were first to report ruthenium complex (40) which catalyses the homogeneous bimolecular disproportionation reaction of aldehydes to give esters. Catalyst (40) was prepared by reacting diphenylacetylene with  $\text{Ru}_3(\text{CO})_{12}$  to give (39) as a colourless solid. Further reaction of (39) with an alcohol lead to the formation of (40) as orange crystalline solid (Scheme 24).

**Scheme 24**

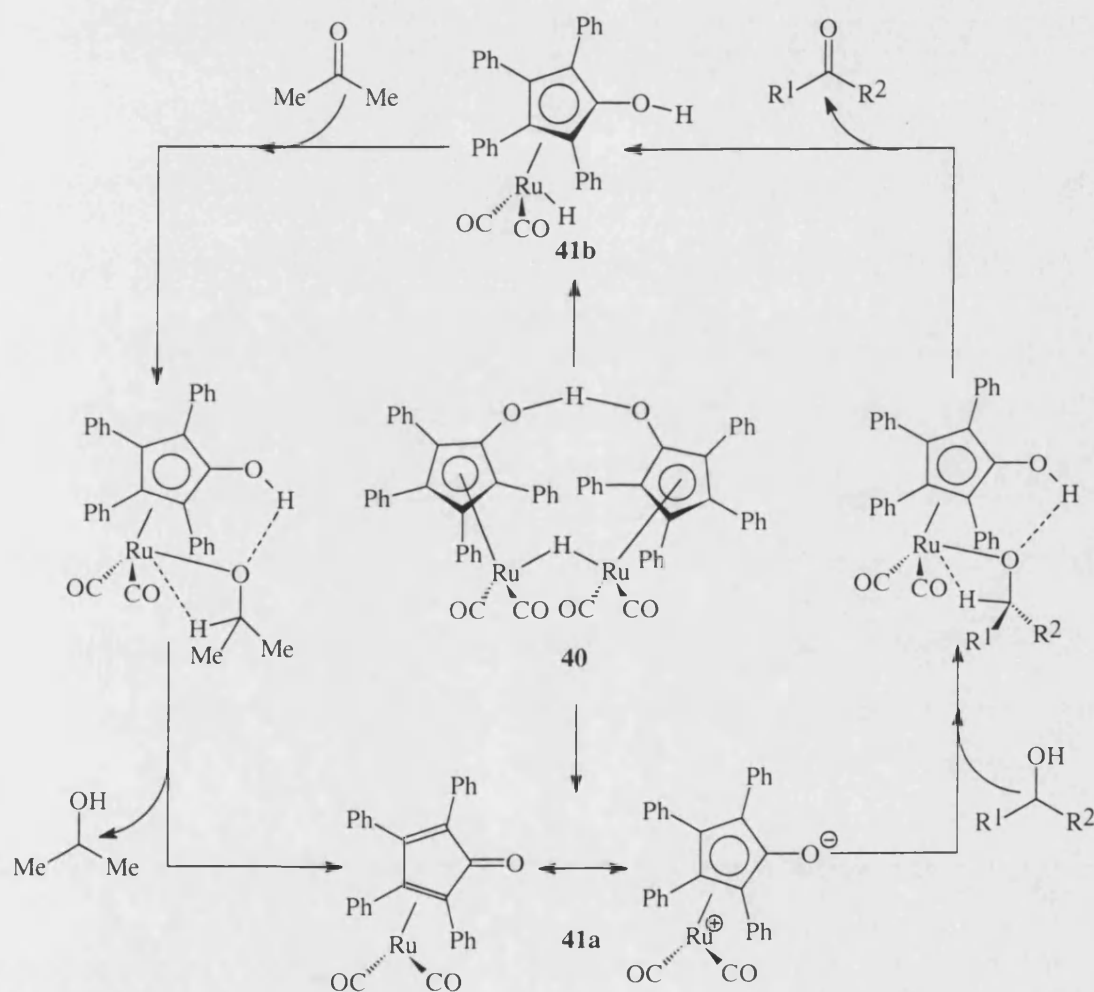


The generated ruthenium dimer (40) was closely followed by Bäckvall *et al.*<sup>75a-b</sup> and they have incorporated this catalyst to conduct an Oppenauer type oxidation of secondary alcohols under mild reaction conditions and without using a base. The interesting feature of catalyst (40) is that it can be divided into two monomeric



species (**41a**) and (**41b**). Since the anionic oxygen of (**41a**) has properties similar to a base, no additional base is required and this monomeric species behaves like an oxidising agent. Species (**41b**) contains a metal hydride and the hydride can be abstracted by a ketone to form the corresponding alcohol, thus performing a reduction reaction (**Scheme 25**).

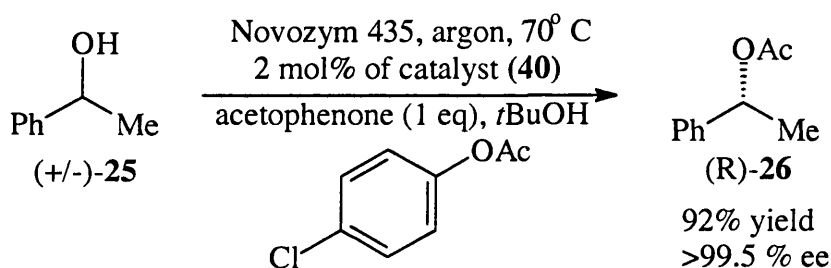
**Scheme 25**



In 1997 Bäckvall *et al*<sup>76</sup> accomplished the DKR of alcohol (**25**) by using the ruthenium dimer (**40**) as the racemising agent. As a consequence this process has the advantage of excluding the addition of a base for the transfer hydrogenation reaction to occur. In this way the interference of an enzymatic resolution by a base was

removed and still maintained the fulfilment required for the oxidation and the reduction processes. The conventionally used vinyl acetate was removed and replaced with chloro-substituted aryl acetates as acyl donors, since vinyl acetate was a poor acyl donor due to the formation of acetaldehyde that acts as an irreversible hydride acceptor, thus oxidising the substrate alcohol to ketone. The DKR of alcohol (**25**) was performed (**Scheme 26**) using catalyst (**40**) (2 mol%), Novozym 435<sup>®</sup>, *p*-chloro-aryl acetate and acetophenone (**27**) (1 eq) at 70 °C in *t*-BuOH to give (R)-**26** in 92% yield with >99% ee. Bäckvall's work was published after our own results had been obtained (see chapter 2).

**Scheme 26**



### B.1.6 Iridium Catalysts

A publication by Pfaltz and co-workers<sup>77</sup> has pointed out that an Ir(I) catalyst prepared *in situ* from [Ir(cod)Cl]<sub>2</sub> and enantiomerically pure bisoxazoline ligands was found to catalyse the transfer hydrogenation of ketones in refluxing IPA with a catalytic amount of KOH. Enantioselective hydrogenation of imines using chiral iridium catalysts was also cited.<sup>78</sup> The reduction of alkyl aryl ketones to the corresponding secondary aryl alcohols (**Scheme 27**) by transfer hydrogenation with IPA and [Ir(cod)NNR\*]ClO<sub>4</sub>/KOH catalyst systems were also successful (NNR\* = pyridinalimine, or Schiff base).<sup>58b,79</sup>

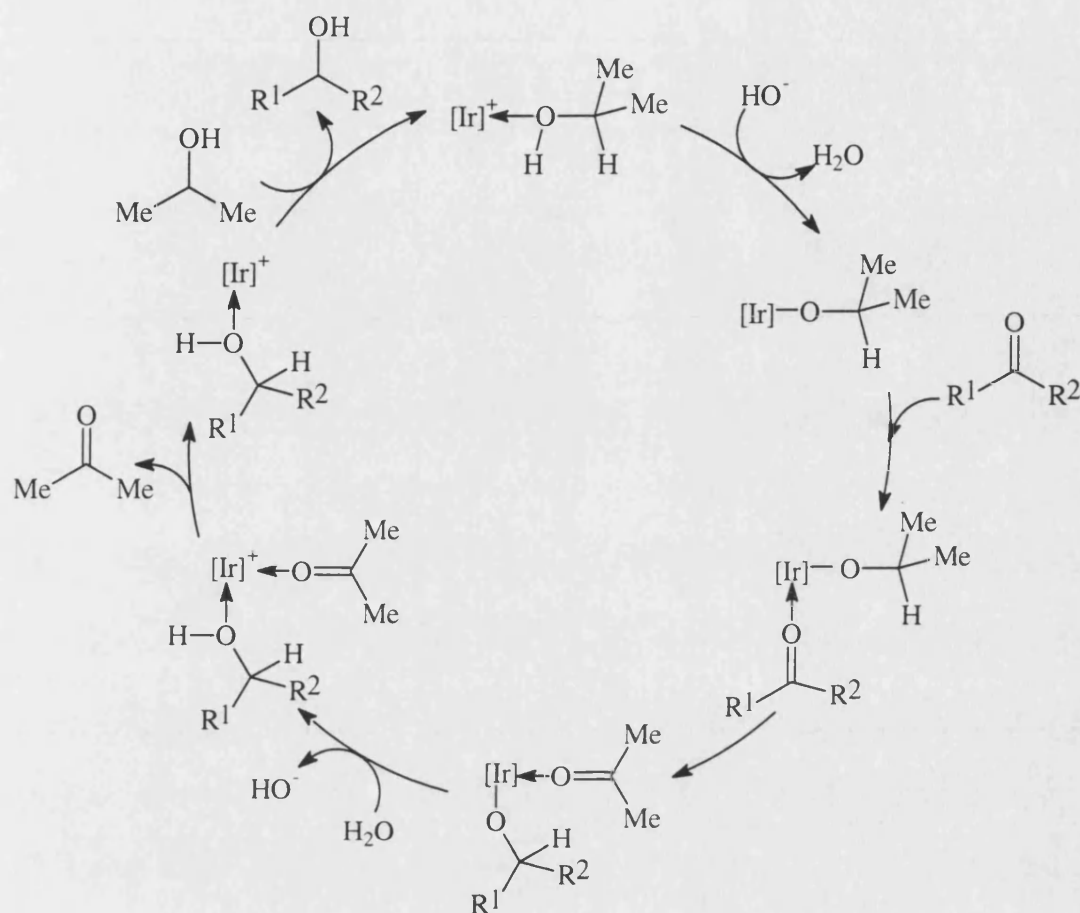
### Scheme 27



R = Me, Et, *n*-Pr, *i*-Pr, *t*-Bu, Bn

Similar to rhodium and ruthenium metal catalysts,<sup>51,80</sup> iridium-catalysed asymmetric transfer hydrogenation reactions were greatly tested with chiral phosphine<sup>56a,81</sup> and nitrogen ligands.<sup>82a-d</sup> Activation of iridium pre-catalysts to displace the co-ordinated cod group was necessary. This procedure was accomplished by air oxidation of IPA solutions at room temperature, followed by refluxing under an argon atmosphere in the presence of a catalytic amount of KOH. A deep blue solution indicates inactive iridium complexes resulting from inappropriate pre-treatment of the catalyst. The catalytic activity was depending on the concentration of KOH because when [KOH]/[catalyst] = 5 [substrate]/[catalyst] = 16250, no activity was observed. The decrease in reaction temperature also decreases the rate of reaction, however, good catalytic activity was still observed even at room temperature. In accordance with the suggested mechanism<sup>51</sup> (**Scheme 28**) for the reduction of ketones using iridium bidentate complexes the hydrogen transfers directly from the isopropoxy to the ketone through a six-centre transition state similar to that proposed for the Meerwein-Ponndorf-Verley-Oppenauer type reaction. The rate-determining step was considered to be the hydrogen transfer from the donor to the acceptor molecule.

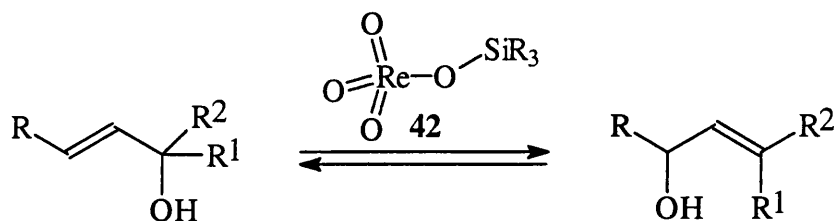
**Scheme 28**



### B.1.7 Racemisation of Secondary Alcohols

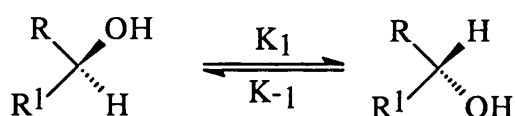
The racemisation of an enantiomerically pure alcohol seems like a chaotic idea after lengthy discussions about asymmetric reduction of prochiral ketones. Osborn *et al*<sup>83a-b</sup> have demonstrated the isomerisation of allyl alcohols (**Scheme 29**) by certain high oxidation state transition metal oxo complexes, especially  $[\text{ReO}_3(\text{OSiR}_3)]$  complex (**42**) which was shown to be active under mild reaction conditions. Industrially  $[\text{VO}(\text{OR})_3]$  or  $[\text{WO}(\text{OR})_4]$  catalysts have been used at high temperatures (ca. 130–200°C) for the production of terpenic alcohols,<sup>84</sup> thus a lower reaction temperature is desirable.

### Scheme 29



Gladysz *et al*<sup>85a-c</sup> have published a large number of papers on rhenium catalysts. In particular the epimerisation of secondary alcohols (**Scheme 30**) catalysed by rhenium(I) methoxide complex of the formula  $(\eta^5\text{-C}_5\text{R}_5)\text{Re}(\text{NO})(\text{PPh}_3)(\text{OMe})$ .

### Scheme 30

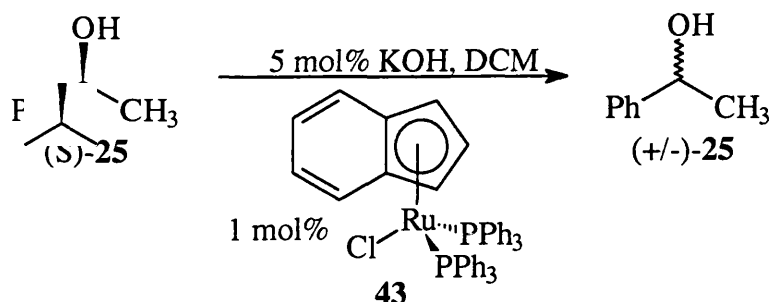


R, R<sup>1</sup> contains an additional stereocentre: epimerisation (interconversion of diastereomers)

R, R<sup>1</sup> contains no additional stereocentre: racemisation (interconversion of enantiomers)

With developing interests in the resolution of racemic alcohols by enzymes coupled with *in situ* racemisation reactions, an efficient catalytic racemisation of secondary alcohols was reported in 1998 by a group in Korea.<sup>86</sup> The racemisation of alcohol (S)-**25** was achieved using  $(\eta^5\text{-indenyl})\text{RuCl}(\text{PPh}_3)_2$  (**43**) within 20 minutes at room temperature in the presence of a strong base (**Scheme 31**).

**Scheme 31**



## C.1.0 Dynamic Kinetic Resolutions

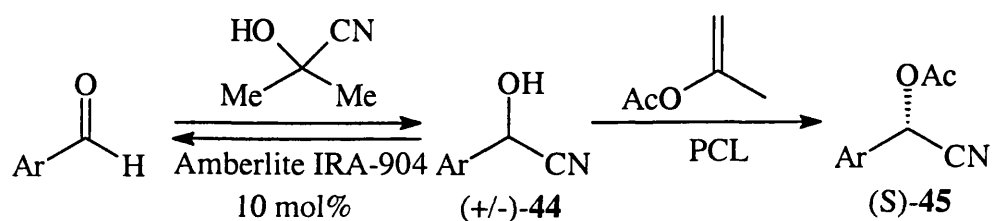
### C.1.1 Introduction

Classical resolution of racemic compounds mediated by enzymes has been a valuable tool for the synthesis of non-racemic products. It is only in the last decade that enzymatic resolution reactions have been modified to become more efficient. This was accomplished by racemising the unreacted enantiomer *in situ* and re-submitting into the enzymatic resolution reaction, only then could a >50% conversion with high enantiomeric purity be obtained. The process is known as a dynamic kinetic resolution (DKR). The concept has been used for 5-hydroxy-5*H*-furan-2-one, pyrrolinone<sup>87</sup> and hemiacetal<sup>88</sup> which are spontaneously racemising while serving as substrates in kinetic resolutions using lipase immobilised on Hyflo Super Cell (HSC). Similarly the deracemisation reactions by stereoinversion of racemic starting materials can give 100% conversion to the enantiomerically pure products.<sup>89</sup> Recently Faber and co-workers<sup>90</sup> have reviewed the dynamic resolutions and stereoinversions using biocatalysts and other dynamic kinetic resolution reviews have been compiled by Caddick and Jenkins<sup>91</sup> and by Ward.<sup>92</sup>

### C.1.2 Racemisation Procedures Coupled With Enzymatic Resolutions

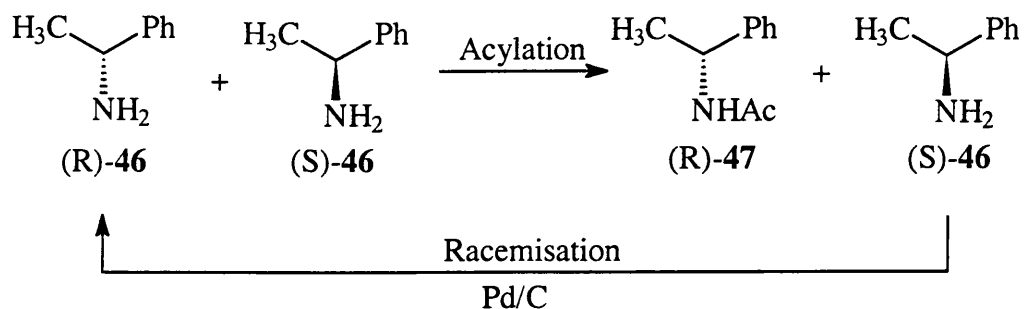
A one-pot generation of enantiomerically pure cyanohydrin acetates (**45**) up to 94% ee in 63-100% conversion was developed<sup>93</sup> using lipase-catalysed kinetic resolution coupled with *in situ* racemisation reaction (**Scheme 32**). Cyanohydrins (**46**) undergo facile racemisation by reversible addition of acetone cyanohydrin to a carbonyl group through transhydrocyanation in diisopropyl ether and catalysed by a strongly basic anion-exchange resin, Amberlite IRA-904 (OH<sup>-</sup> form). Whereas the acetylated product (**45**) does not racemise under the same reaction conditions.

**Scheme 32**



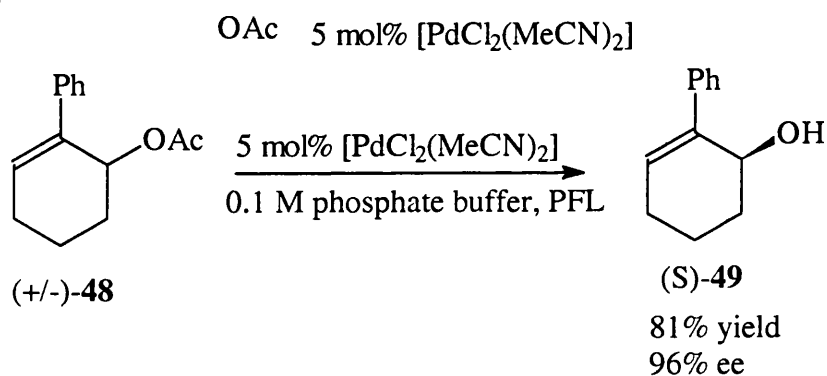
Reetz *et al*<sup>94</sup> have reported the DKR of phenylethylamine (**46**) using palladium catalyst (racemising agent) and lipase Novozym SP435<sup>®</sup> in the presence of ethyl acetate as the acylating agent. Palladium-catalysed racemisation of chiral amines was shown to be compatible with lipase-catalysed enantioselective *N*-acylation reaction. The *N*-acylated product (R)-**47** was obtained in 75-77% conversion (ee = 99%) (**Scheme 33**).

### Scheme 33



Williams *et al*<sup>95</sup> have also demonstrated palladium-catalysed racemisation of allylic acetates by [3,3]-sigmatropic rearrangements in the presence of a lipase enzyme. The enantioselective hydrolysis of the substituted allyl acetate (**48**) by PFL in phosphate buffer with 5 mol% palladium complex gave the allylic alcohol, (S)-**49**, in 96% conversion (81% isolated yield) and 96% ee after 19 days (Scheme 34).

### Scheme 34





## **Chapter 2**

## **D.1.0 Results and Discussions**

### **D.1.1 Introduction**

As the millennium is approaching science and technology have advanced at an incredible rate. The future will have to face modern diseases and scientists will have to develop new drugs quickly and efficiently. Therefore the synthesis of these drugs will require facile procedures that are elegant and simple. Not long ago drugs were synthesised as a racemate but now the syntheses of enantiomerically pure compounds have become customary. The preparation of an enantiomerically enriched molecule that requires stereochemistry can often cause many problems such as, high cost, low stereoselectivity and poor yields. Modern organic chemistry offers a wide choice of synthetic methods and a cargo of reagents to choose from. Despite the widely available resources, asymmetric methods for producing enantiomerically pure compounds have been expensive and inefficient.

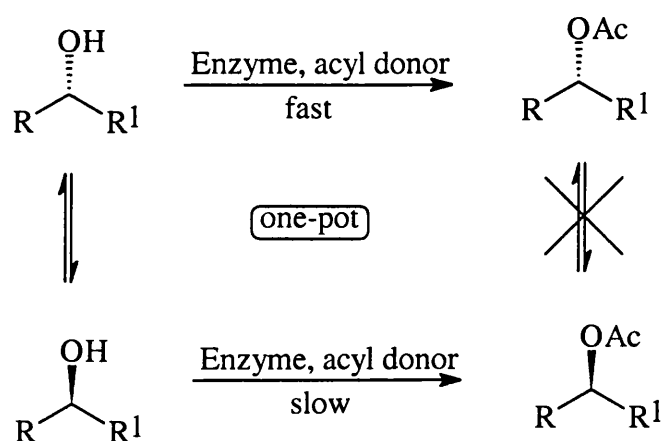
Suppose that there is a powerful tool for organic chemists to produce enantiomerically pure compounds with ease. Wouldn't that be great if there is such a powerful tool? A tool that is simple, inexpensive, efficient and environmentally safe. Why not take a look at nature? A closer look, at a molecular level to see how Mother Nature does things and to do them so efficiently and effectively. All the biological functions in living organisms are catalysed by enzymes and scientists have been using these enzymes to resolve many racemic compounds. Enzymatic resolutions, however, only convert a maximum of 50% of the starting material based on the racemate. One way of tackling the unreacted enantiomer is by recycling. The recycling process is usually a racemisation procedure that interconverts the remaining enantiomer into a racemate. Normally the racemisation processes will require

isolation of the component, followed by harsh treatments such as strong bases or acids and high temperatures.

### D.1.2 Aims

Enzyme-catalysed hydrolysis of esters and enzyme-catalysed acylation of alcohols are the most commonly known processes.<sup>1,14</sup> The hydrolysis of esters occurs under aqueous buffer conditions and the acylation of alcohols can be performed in organic solvents with a suitable acyl donor. The project aim concentrates on the dynamic kinetic resolution (DKR) of secondary alcohols by coupling an enzymatic resolution reaction with a racemising agent. A simple kinetic resolution of a racemic alcohol will only give half of the product and the remaining half is unreacted. By racemising the unreacted alcohol *in situ* coupled with an enzymatic resolution reaction, the process will enable a possible 100% conversion into the enantiomerically enriched product (Scheme 35).

Scheme 35



The racemisation of a secondary alcohol requires a metal catalyst that will temporarily oxidise the alcohol into the corresponding ketone by a hydride transfer mechanism. The racemisation process, if successful, will be coupled with an

enzymatic resolution reaction to effect a DKR. To achieve an ideal DKR, several criteria have to be fulfilled. Enzymes are delicate species and any harsh treatments such as large pH changes, high temperatures and any source of inhibitors will result in deactivation or retardation of the enzyme. Therefore the choice of a metal catalyst is narrow and a mild racemisation condition is required. The metal catalyst must not racemise the acetate product or catalyse the acylation reaction, otherwise the enantioselectivity of the product formation will be lost. Therefore any metal catalysts that promote the chemical acylation reactions will be excluded. Also the metal catalyst and any added reagents, or the by-products formed must not interfere with the enzyme and *vice versa*. Potentially both the enzyme and the metal catalyst must operate in harmony in the same environment.

The racemisation investigations will involve the use of a single enantiomer of the (R)- or (S)-1-phenylethan-1-ol, (R)- or (S)-**25**, costing ~£40/g and will be racemised to produce a racemic mixture costing ~£1/g. Despite the chaotic and uneconomical approach, a successful DKR will be far more appreciable and desirable than any other asymmetric methods already existed. Of course, the project aim is to design a DKR method that is applicable to any secondary alcohol.

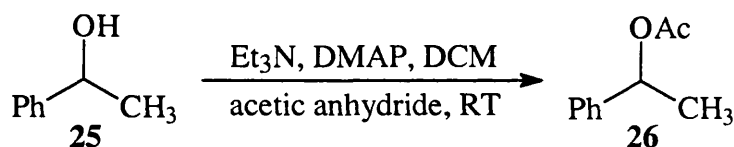
### D.1.3 Enzyme-Catalysed Acylation Reactions

Lipase enzymes have been well known<sup>1,14</sup> to catalyse the acylation reaction of an alcohol in the presence of an acyl donor. With extensive knowledge in this area, the first strategy was to screen a number of lipase enzymes that are commercially available. Vinyl acetate was chosen because it has a dual function, acting as a solvent and as an acyl donating agent.<sup>19,20,34</sup> The ideal substrate would be alcohol (**25**)

because it contains a large phenyl and a small methyl group at the chiral centre. A large difference in the substituents will implement a high enantioselectivity. When the methyl moiety was replaced with a cyclopropyl, phenyl, *t*-butyl or heptyl, no acylation was observed.

Before the enzyme screening process could begin, 1-acetoxy-1-phenylethane (**26**) was synthesised by reacting alcohol (**25**) with acetic anhydride (1.1 eq) in the presence of Et<sub>3</sub>N (1.1 eq) and a catalytic amount of DMAP in DCM (**Scheme 36**). The reaction was monitored by TLC and stopped when all the starting material has been used up. After aqueous workup and purifications, the acetate product (**26**) was obtained as a yellow oil in 89% isolated yield.

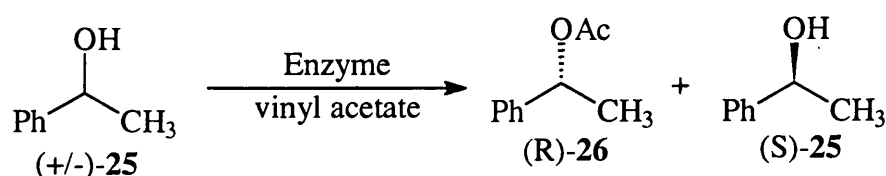
**Scheme 36**



Confirmation of the product (**26**) was supported by IR spectroscopy showing a disappearance of an OH peak at 3355 cm<sup>-1</sup> and an appearance of a strong carbonyl peak at 1743 cm<sup>-1</sup>; <sup>1</sup>H NMR analysis gave a doublet at 1.55 ppm (alcohol doublet appears at 1.49 ppm), a singlet at 2.0 ppm and a quartet at 5.87 ppm (shifted from 4.98 ppm); analysis using HPLC Chiralcel OD column, 99:1 (Hex/IPA), λ = 254 nm, 1mL/min, Rt (R)-**26** = 5.1 min and Rt (S)-**26** = 5.5 min (the absolute configuration was determined by co-injection of an enantiomerically pure acetate (R)-**26** which was synthesised from enantiomerically pure (R)-**25**). The information obtained from (**26**) will be used for future references.

The enzyme screening process was performed using alcohol (**25**), a lipase enzyme and vinyl acetate (Scheme 37). The course of the reaction was monitored by TLC and at the end of the reaction the crude product was obtained by simple filtration through a plug of silica. A large number of different enzymes were used in the screening process and only those that gave good conversions with high enantioselectivities were recorded (Table 1).

**Scheme 37**



**Table 1.** Results obtained for enzyme-catalysed acylation of alcohol (**25**)

Lipase Enzyme	Time (h)	Temp °C	% conv <sup>a</sup>	% ee <sup>b</sup>	Abs. Conf. <sup>c</sup>
<i>Pseudomonas fluorescens</i>	21	40	48.0	>99	R
<i>Pseudomonas fluorescens</i>	45	40	51.0	>99	R
<i>Pseudomonas sp.</i>	24	40	38.0	>99	R
<i>Pseudomonas cepacia</i>	24	50	23.3	100	R

<sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopy. <sup>b</sup> Analysed by chiral HPLC. <sup>c</sup> Determined by comparison with the enantiomerically pure (R)-**26**.

The data in table 1 have shown that lipase from *Pseudomonas fluorescens* (PFL) has resolved the racemic alcohol (**25**) to the acetate (R)-**26** at 48% conversion in >99% ee after 21 hours at 40 °C. Both the substrate (**25**) and the product (**26**) can be resolved by chiral HPLC under the same conditions (Chiralcel OD column, 99:1 (Hex/IPA), 1 mL/min, λ = 254nm). The retention times for the (S)- and (R)- alcohols were 18.4 min and 24.0 min, respectively. The acetate (R)-**26** was recorded at Rt = 5.1 min. Conversions were determined using <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) by calculating the

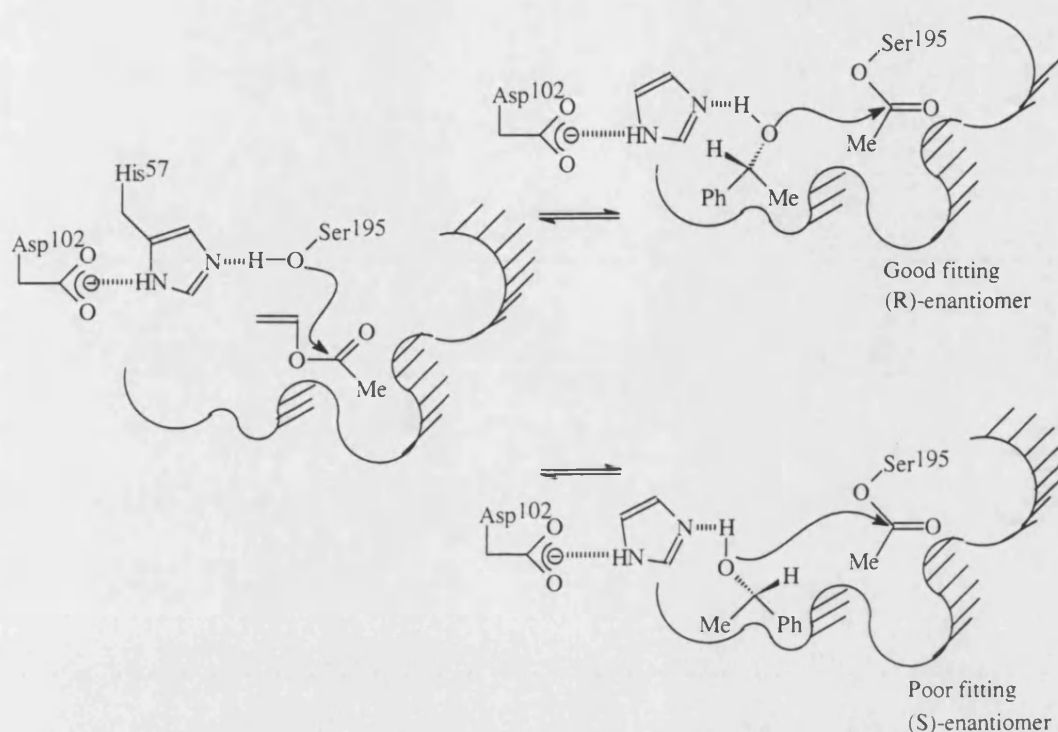
intensity ratio between the alcohol quartet at 4.98 ppm and the acetate quartet at 5.87 ppm.

Other acyl donors were also tested but the reaction rate decreases as the acyl chain length increases.<sup>19</sup> The reactivity of acyl donors is as follows, vinyl acetate>isopropenyl acetate>vinyl butyrate>2,2,2-trifluorobutyrate>vinyl laurate.<sup>20,21</sup>

#### **D.1.4 Proposed Mechanism for Enzyme-Catalysed Acylation Reactions**

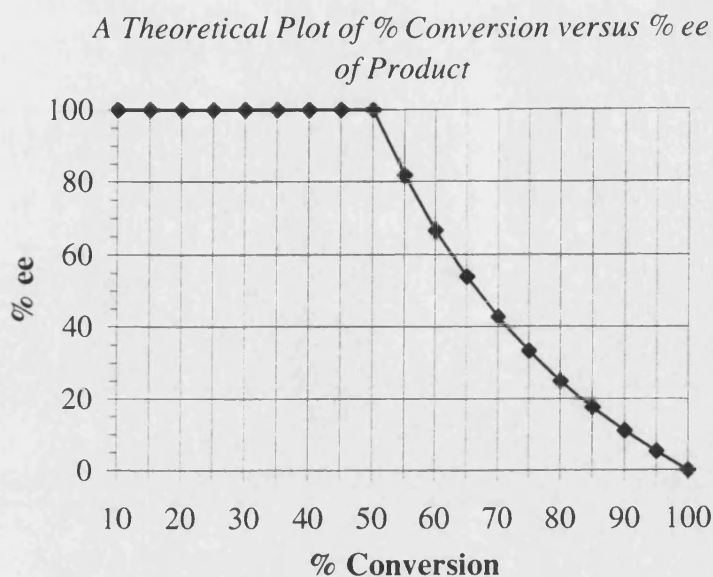
It has been illustrated that enzyme-catalysed acylation reactions favour the (R)-enantiomer<sup>24</sup> but this also depends on the enzyme used. The enantioselectivity of an enzyme depends on the shape and the fitting of substrates in the enzyme active site. Here we have proposed a situation similar to that described in the literature.<sup>27-31</sup> Substrate (**25**) consists of a large phenyl portion and a small methyl portion. The larger group usually occupies the large hydrophobic pocket and a smaller pocket is reserved for a more compact moiety in the enzyme active site (**Scheme 38**). Lipase enzymes are believed to contain these pockets, hence the enantioselectivity observed was extremely high for the acylation of the alcohol (**25**).

**Scheme 38**



The proposed mechanism above also illustrates another important feature that governs the enantioselectivity. In the case where the (R)-enantiomer fits nicely into the enzyme active site, the hydroxyl of (**25**) is held closer towards the serine-acetate complex than the (S)-enantiomer. Bearing this hypothesis in mind, the acylation of (S)-**25** will not take place if the distance between the substrate and the serine-acetate complex is too great and we have found that the reaction went to 48% conversion after 24 hours and only 51% conversion after 45 hours (**Table 1**). These results have supported the analogy because the reaction has stopped at ~50% conversion. A plot illustrating the theoretical percentage enantiomeric excess of product versus the percentage conversion for a simple kinetic resolution is shown below (**Chart 1**).



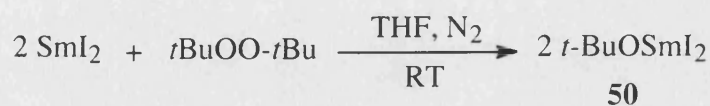


**Chart 1.** A simple kinetic resolution Plot

#### D.1.5 Samarium Species

Samarium alkoxides have been documented as one of the transfer hydrogenation catalysts.<sup>43-45</sup> Samarium *tert*-butoxide (**50**) was prepared by reacting di-*tert*-butyl peroxide in 0.2 M THF solution (1 eq) with samarium(II) iodide in 0.1 M THF solution (2 eq) at room temperature under an inert atmosphere (**Scheme 39**). A colour change occurred immediately, changing from blue-green to yellow. This was an indication for the formation of catalyst (**50**).

#### Scheme 39

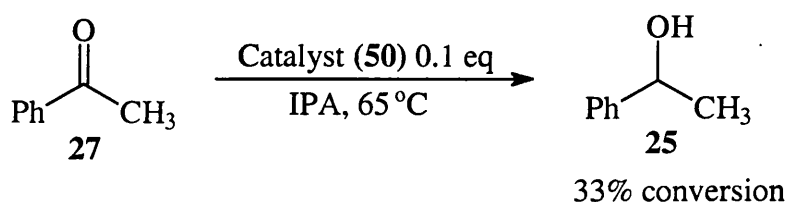


Decomposition of catalyst (**50**) takes place within a two hour period, therefore it must be used immediately once synthesised. Samarium alkoxides are very sensitive to moisture and to minimise any deactivation of the catalyst, strict anhydrous conditions must be enforced.

## Oxidation and Reduction Reactions

Initially, the prepared catalyst was used to reduce acetophenone (**27**) (**Scheme 40**). A typical procedure was the reaction between the freshly prepared solution of samarium catalyst (**50**) (0.1 eq) with acetophenone (**27**) in IPA (1 mL). The reaction mixture was stirred at 65 °C under an inert atmosphere for 5 hours, but the alcohol (**25**) was only obtained in 33% conversion (determined by  $^1\text{H}$  NMR).

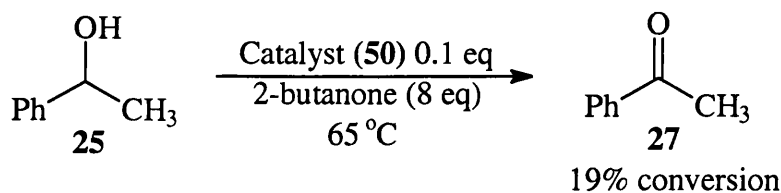
**Scheme 40**



Analyses by IR spectroscopy have supported the formation of the alcohol (**25**) indicated by a sharp OH peak at  $3355\text{ cm}^{-1}$  and  $^1\text{H}$  NMR gave a doublet at 1.49 ppm, a singlet at 2.40 ppm and a quartet at 4.98 ppm. These data were sufficient proof of the presence of alcohol (**25**) and since it is a commercially available compound, no further analyses were necessary.

Similarly the oxidation of the alcohol (**25**) by catalyst (**50**) (0.1 eq) in 2-butanone (8 eq) only gave 19% conversion after 68 hours at 65 °C (**Scheme 41**). The conversion obtained was discouraging when compared with an oxidation reaction performed under the same conditions by Kagan and co-workers,<sup>43a-b</sup> ketone (**27**) was obtained in 98% yield after 24 hours.

#### Scheme 41

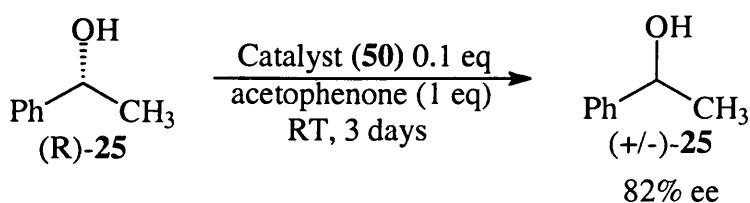


Several attempts were tried but at best the conversion achieved was ~33%. Justifications for the low conversions could be due to catalyst deactivation over time caused by air and moisture.

#### Racemisation Reactions

Irrespective of the low conversions observed, the catalyst (50) has promoted the oxidation and the reduction reactions. The catalyst (50) was then used for the racemisation of (R)-25 in the presence of acetophenone (27) (1 eq) at room temperature. (Scheme 42). After 3 days the recovered alcohol was obtained in 82% ee (analysed by chiral HPLC). Obviously some racemisation has occurred.

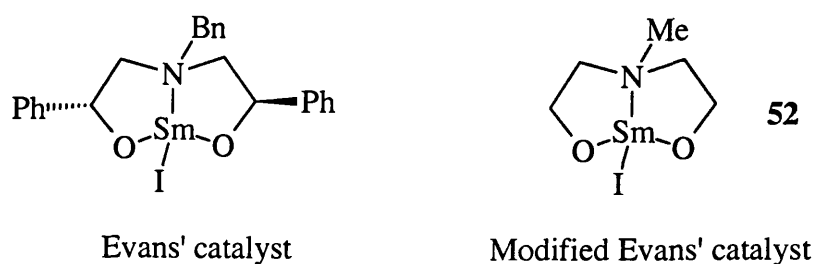
#### Scheme 42



Since the rate of racemisation using the catalyst (50) was slow, other catalysts were considered. Evans and co-workers<sup>46</sup> have described an active samarium species that operates at ambient temperature. In their report, acetophenone (27) was reduced to the alcohol (25) using Evans' catalyst in IPA (25 eq) at room temperature for 24

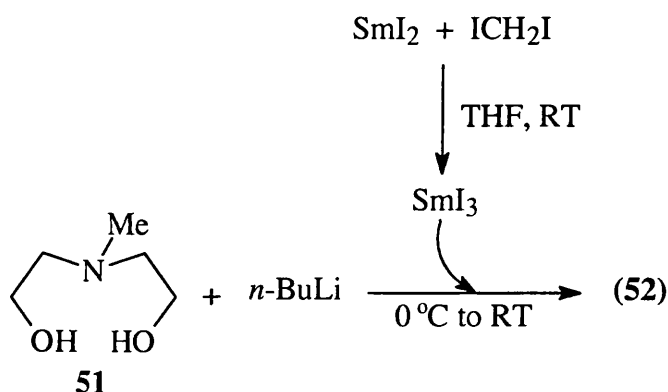
hours, 83% conversion in 96% ee was achieved. Our objective was to racemise secondary alcohols, therefore enantioselectivity was not required. Hence we have modified Evans' catalyst by removing the two chiral centres (**Scheme 43**).

**Scheme 43**



The modified Evans' catalyst (**52**) was prepared by treating samarium(II) iodide (2 eq) with diiodoethane (1 eq) under an inert atmosphere at room temperature to give the subsequent product, samarium(III) iodide. In a second flask containing *N*-methyl ethanolamine (**51**) (1 eq) in THF under a nitrogen atmosphere at 0 °C, *n*-BuLi (1.9 eq) was added dropwise. Then samarium(III) iodide was transferred *via* a cannula to the *O*-lithiated *N*-methyl diethanolamine mixture under a positive nitrogen pressure. The formation of catalyst (**52**) was indicated by an orange solution (**Scheme 44**). No analysis was made because catalyst (**52**) is highly unstable in air.

**Scheme 44**



The reduction of the ketone (**27**) was examined using the freshly made catalyst (**52**) (0.1 eq) and an excess amount of IPA, but no conversion was observed (analysed by TLC).

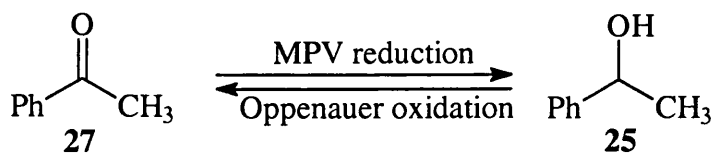
Further studies were carried out using samarium catalysts; when combined with an enzyme, however, in a one-pot reaction, a complex NMR spectrum was observed. The data have indicated that samarium catalysts and lipase enzymes were incompatible when coupled together.

#### D.1.6 Aluminium Alkoxides

##### Oxidation and Reduction Reactions

Aluminium alkoxides have been known to carry out hydride transfer reversibly to a carbonyl acceptor.<sup>38,39,43a-b,47-49</sup> Aluminium isopropoxide can be readily obtained and the catalyst can be used to promote the MPV reduction and Oppenauer oxidation reactions. The reduction reaction requires a reductant, commonly IPA, and for the oxidation reaction an oxidant (2-butanone) is required (**Scheme 45**).

**Scheme 45**

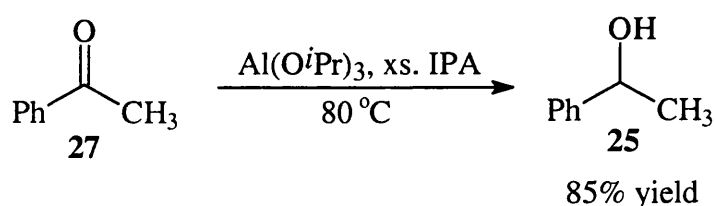


MPVO reactions were performed at 40 °C to coincide with the enzymatic resolution reactions. The reduction of ketone (**27**) was unsuccessful and the oxidation of the alcohol (**25**) only gave very small traces of the ketone at this temperature (determined by <sup>1</sup>H NMR spectroscopy and by TLC). The experiments were repeated with an

addition of a small amount of sodium *tert*-butoxide to the reactions. There were, however, no significant improvements on the reaction rate to be taken into account.

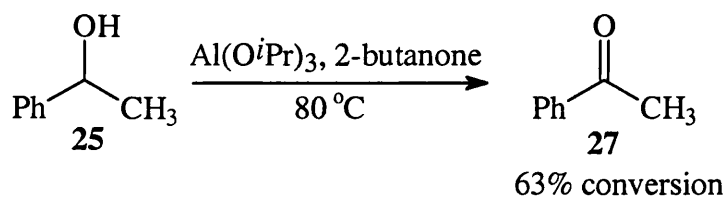
The oxidation and reduction potential of different substrates have been discussed in chapter 1 and the reaction conditions were shown to be dependant on these factors.<sup>39</sup> The reduction of acetophenone (**27**) was then performed at an elevated temperature of 80 °C, catalysed by aluminium isopropoxide (0.1 eq) in the presence of excess amount of IPA and after 20 hours 85% yield of the alcohol (**25**) was obtained (Scheme 46). The product was analysed by TLC using 2:1 (petroleum ether/ether) and only a single spot was observed at  $R_f = 0.28$ ; IR spectrum displayed no OH peak at  $3355\text{ cm}^{-1}$  but a conjugated carbonyl peak at  $1684\text{ cm}^{-1}$  was observed;  $^1\text{H}$  NMR data did not show any peaks corresponding to the ketone (**27**); HPLC Chiralcel OD column, 99:1 (Hex/IPA), 1mL/min,  $\lambda = 254\text{ nm}$ , gave  $R_t$  (R)-**25** = 18.5 min and  $R_t$  (S)-**25** = 25.3 min (coincided with the retention times of alcohol (**25**) purchased).

Scheme 46



The Oppenauer oxidation reaction of the alcohol (**25**) with aluminium isopropoxide (0.1 eq) and 2-butanone (2 eq) was also performed at 80 °C. After acidic work up, the pale yellow oil was obtained in 63% conversion (determined by  $^1\text{H}$  NMR) (Scheme 47). The formation of the ketone (**27**) was supported by TLC, IR and  $^1\text{H}$  NMR data.

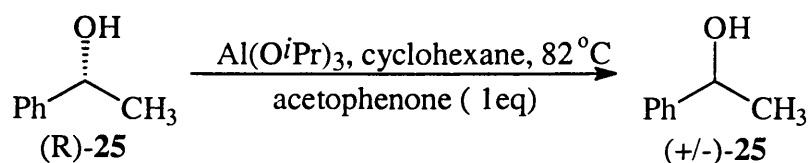
## Scheme 47



## Racemisation Reactions

The MPV reduction and the Oppenauer oxidation reactions have been successfully achieved and the next logical plan was to pursue the racemisation of an enantiomerically pure alcohol. A single enantiomer of the alcohol (R)-**25** was racemised under conditions containing aluminium isopropoxide (0.1 eq), acetophenone (**27**) (1 eq) and cyclohexane at 82 °C (Scheme 48). The reaction mixture was stirred for 24 hours and the alcohol (R)-**25** was recovered in 87% ee, and then only 5% ee after 72 hours (Table 2).

## Scheme 48



**Table 2.** Racemisation of the alcohol (R)-**25** using aluminium isopropoxide

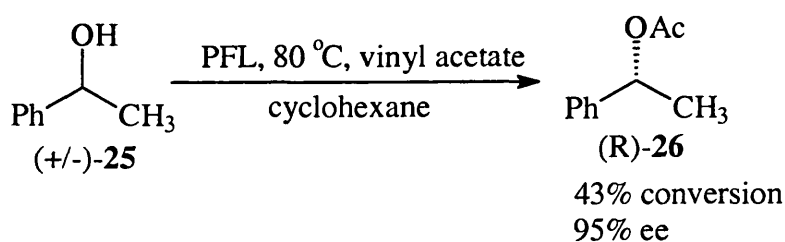
Entry	Time (h)	% ee <sup>a</sup>
1	0	>99
2	24	87
3	72	5

<sup>a</sup>Analysed by chiral HPLC.

## Dynamic Kinetic Resolution Reactions

It was rewarding to have achieved the two main objectives soon after starting the project. Nevertheless the obstacles ahead were to become more challenging and difficult. Since the racemisation reaction only works above 80 °C, this was an apparent problem when combined with an enzymatic resolution reaction. Bearing this in mind, an acylation reaction of the alcohol (**25**) was set up using PFL and vinyl acetate/cyclohexane (2:1) at 80 °C (**Scheme 49**). After 24 hours the reaction mixture was filtered through a plug of silica to remove the enzyme and the acetate product (**(R)**-**26**) was collected at 43% conversion with 95% ee, analysed by <sup>1</sup>H NMR and chiral HPLC.

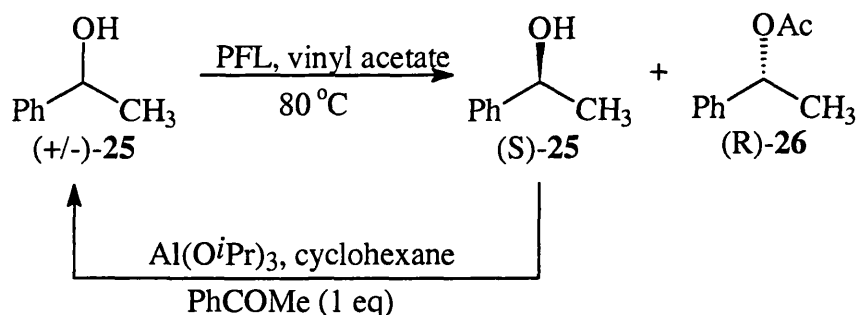
**Scheme 49**



The two objectives have been accomplished. The question is can we put them together? An attempted DKR reaction was assembled by adding the racemic alcohol (**25**), the acetophenone (**27**) (1 eq), aluminium isopropoxide (0.1 eq), excess amount of vinyl acetate, cyclohexane and PFL, all in a single reaction vessel. The reaction concoction was stirred at 80 °C and aliquots were taken at different intervals for HPLC analysis (**Scheme 50**). The results obtained displayed a decrease in enantiomeric purity as the conversion was increased. Yet the enantiomeric excess of the alcohol (**25**) was fluctuating, indicating an *in situ* racemisation process (**Table 3**).



Scheme 50

Table 3. Attempted DKR reaction using  $\text{Al}(\text{O}^i\text{Pr})_3$  and PFL

Time (days)	% conversion <sup>a</sup>	% ee (R)-26 <sup>b</sup>	% ee (S)-25 <sup>b</sup>
5	59	37	10
10	71	28	98
11	82	13	84

<sup>a</sup>Determined by  $^1\text{H}$  NMR. <sup>b</sup>Analysed by chiral HPLC.

Investigations were carried out to optimise the conditions but at best the results obtained were 57-82% conversion with 33-78% ee (Table 4).

Table 4. Aluminium-catalysed racemisation coupled with enzyme-catalysed acylation

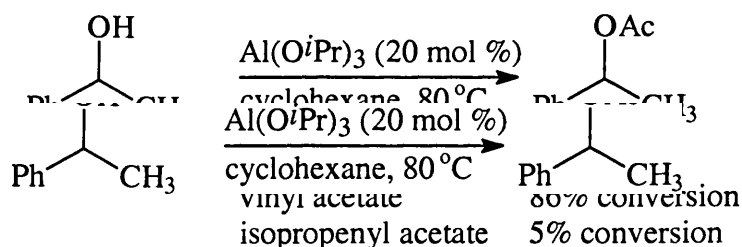
Entry	Time (days)	% conversion <sup>a</sup>	% ee (R)-26 <sup>b</sup>	% ee (S)-25 <sup>b</sup>
1	6 <sup>c</sup>	82	33	-
2	7	70	47	-
3	5 <sup>d</sup>	69	65	100
4	3 <sup>e</sup>	62	71	88
5	8	57	78	-

<sup>a</sup> Determined by  $^1\text{H}$  NMR. <sup>b</sup> Analysed by chiral HPLC. <sup>c</sup>  $\text{Al}(\text{O}^i\text{Pr})_3$  was added to the enzyme reaction after 24 hours. <sup>d</sup>  $\text{Al}(\text{O}^i\text{Pr})_3$  (20 mol%), PhCOMe, PFL, vinylacetate/methyl cyclohexane (2:1) were added to the enzyme reaction after 24 hours. <sup>e</sup>  $\text{Al}(\text{O}^i\text{Pr})_3$  and activated Amberlite were added after 24 hours.

The results obtained in table 4 have indicated that as the conversion increases, the enantioselectivity decreases. Therefore a simple kinetic resolution reaction of the

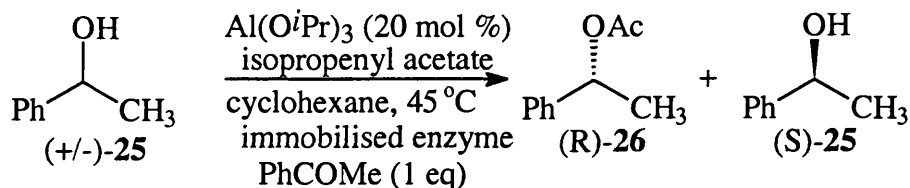
alcohol (**25**) was set up to investigate the situation. After 6 days the acetate product (R)-**26** was obtained in 56% conversion with 86% ee. The same reaction was repeated with an addition of aluminium isopropoxide (0.1 eq) and after 24 hours, the acetate (R)-**26** was obtained in 56% conversion with only 24% ee and the alcohol (**25**) was recovered in 28% ee. So it can be concluded that aluminium alkoxide has aided the acylation reaction. Also another test reaction was conducted using the alcohol (**25**), vinyl acetate, aluminium isopropoxide and without an enzyme. The results recorded have found that aluminium isopropoxide had catalysed the acylation reaction to give 86% of the acetate (**26**), analysed by  $^1\text{H}$  NMR. When vinyl acetate was replaced with isopropenyl acetate the product (**26**) was reduced down to 5% showing the formation of the racemic acetate (**26**) was suppressed (**Scheme 51**).

**Scheme 51**



The DKR reactions were performed using the racemic (**25**),  $\text{Al}(\text{O}^i\text{Pr})_3$  (20 mol%), isopropenyl acetate and an immobilised enzyme in cyclohexane (**Scheme 52**). The best conversion observed was 60% with >99% ee (**Table 5**). Isopropenyl acetate gives off acetone as a by-product which is less reactive than acetaldehyde (a by-product of vinyl acetate) and acetaldehyde has been shown to inhibit enzyme activities.

## Scheme 52



**Table 5.** Attempted DKR using  $\text{Al}(\text{O}^i\text{Pr})_3$ , isopropenyl acetate and immobilised enzyme

Entry	Enzyme	Time (days)	% Conv <sup>a</sup>	% ee (R)- <b>26</b> <sup>b</sup>	% ee (S)- <b>25</b> <sup>b</sup>
1	CAL	5	55	>99	-
2	Novo SP435	4	53	100	100
3	PFL	5	53	>99	-
4	PFL <sup>c</sup>	4	60	>99	100

<sup>a</sup> Determined by  $^1\text{H}$  NMR. <sup>b</sup> Analysed using chiral HPLC. <sup>c</sup> Crude enzyme was used.

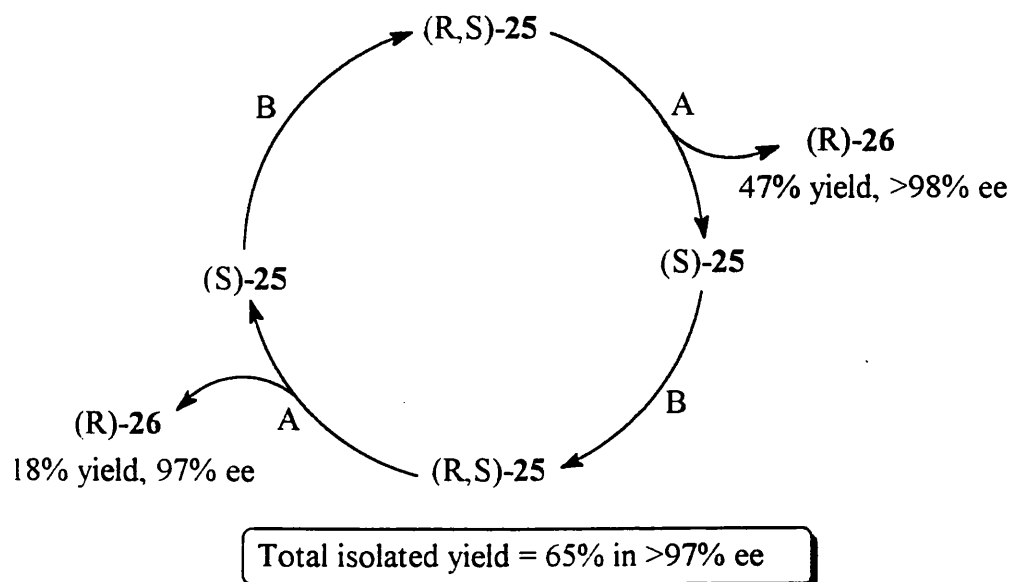
In all cases the enantioselectivity was high, although acetate (R)-**26** was best attained at 60% conversion. Nevertheless, isopropenyl acetate has avoided the chemical acylation problem caused by aluminium isopropoxide and high enantiomeric purity of the product (R)-**26** was restored.

## Iterative Procedure

This method involves an enzymatic acylation reaction, isolation of the acetate product (R)-**26** and then racemisation of the unreacted alcohol (S)-**25** using a catalytic amount of  $\text{Al}(\text{O}^i\text{Pr})_3$ . After the racemisation process, the racemic alcohol (**25**) was purified, then re-submitted for an enzymatic resolution reaction (Scheme 53). The procedure could be repeated several times until a maximum obtainable yield was achieved. For the purpose of demonstrating the principle of this strategy, only

two cycles were performed to give the acetate (R)-26 in 65% isolated yield with >97% ee.

### Scheme 53



Experimental conditions:

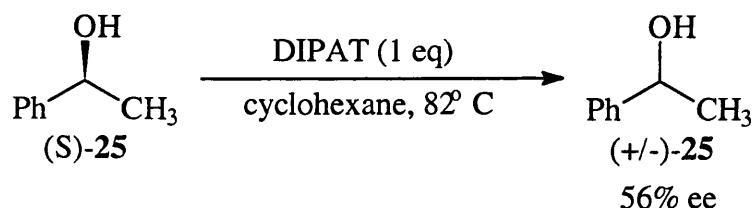
A = Lipase from *Pseudomonas fluorescens*, vinyl acetate, 40 °C, 24 hours.

B = Al(O<sup>i</sup>Pr)<sub>3</sub> (20 mol %), PhCOMe (1 eq), cyclohexane, 80 °C, 72 hours.

### Reactions With DIPAT

Diisopropylaluminium trifluoroacetate (DIPAT) has been described<sup>49,50</sup> as a very efficient catalyst for the oxidation of alcohols by *p*-nitrobenzaldehyde (PNB). DIPAT was synthesised as described<sup>49</sup> in the literature to give a white powder in 64% yield with a melting point decomposition >220 °C (in agreement with the literature value). The racemisation of the alcohol (S)-25 was carried out using a stoichiometric amount of DIPAT in cyclohexane at 82 °C. After 48 hours, the alcohol (S)-25 was recovered in 56% ee (analysed by chiral HPLC) (Scheme 54).

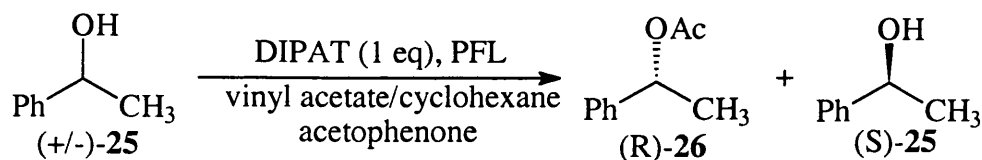
#### Scheme 54



The racemisation of (S)-25 was exploited and found that a stoichiometric amount of DIPAT was necessary to attain a good racemisation rate. When the alcohol (S)-25 was racemised by DIPAT (0.2 eq) and the acetophenone (27) (1 eq), only 70% ee of the alcohol (S)-25 was recovered after 3 days.

Attempted DKR reactions using DIPAT also gave low enantioselectivity similar to those obtained using aluminium isopropoxide. The DKR reactions were performed by adding the alcohol (25), the acetophenone (27) (1 eq), DIPAT (1 eq), PFL, vinyl acetate and cyclohexane (2:1) to an ace-pressure tube, sealed, and stirred with heating (Scheme 55). Aliquots were removed during the course of the reaction and analysed using chiral HPLC. The results obtained (Table 6) were 59-77% conversions and 35-66% ee.

#### Scheme 55



**Table 6.** DKR reactions using DIPAT catalyst

Time (days)	Temp °C	% conv	% ee (R)-26 <sup>a</sup>	% ee (S)-25 <sup>a</sup>
3 <sup>b</sup>	80	35.3	73.6	38.6
7	80	57.3	72.9	35.0
4 <sup>c</sup>	60	58.9	66.1	100
10	60	77.4	34.8	100

<sup>a</sup> Analysed by chiral HPLC. <sup>b</sup> More PFL (15 mg) was added after 3 days. <sup>c</sup> DIPAT and acetophenone (**27**) were added to the enzyme reaction after 24 hours and more enzyme was added after 3 days.

It was later found that DIPAT also catalyses the acylation reaction and other metal catalysts were then considered.

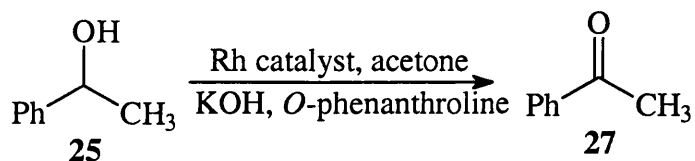
#### D.1.7 Rhodium Catalysts

Here we have invested in the three most commonly known rhodium pre-catalysts, [Rh(cod)Cl]<sub>2</sub>, Rh<sub>2</sub>(OAc)<sub>4</sub>.2H<sub>2</sub>O and [Rh(hd)Cl]<sub>2</sub>. Information gathered from published<sup>53-60</sup> reports have shown that ligands have prolonged the catalyst activity and the presence of a strong base<sup>52</sup> was essential for the transfer hydrogenation process. The sole purpose of this project is the racemisation of secondary alcohols. Therefore, achiral *O*-phenanthroline ligand was used.

#### Oxidation and Reduction Reactions

Rudimentary studies were concentrated on the oxidation of the alcohol (**25**) using acetone as the oxidant. The catalyst was activated by stirring ligand/rhodium (4:1) together in excess acetone for 15 minutes before the alcohol (**25**) and KOH were added (Scheme 56).

### Scheme 56



**Table 7.** Rhodium-catalysed oxidation of alcohol (**25**)

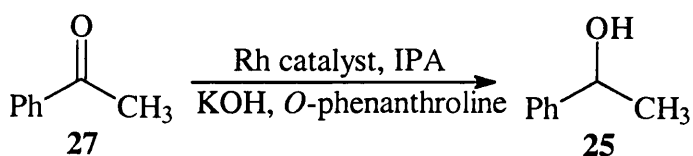
Entry	Catalyst (mol%)	KOH (mol%)	Temp °C	Time (h)	% conv <sup>a</sup>
1	[Rh(cod)Cl] <sub>2</sub> (2.0)	20	70	2	61
2	[Rh(cod)Cl] <sub>2</sub> (2.0)	20	80	1	63
3	Rh <sub>2</sub> (OAc) <sub>4</sub> .2H <sub>2</sub> O (1.0)	5	60	72	20
4	Rh <sub>2</sub> (OAc) <sub>4</sub> .2H <sub>2</sub> O (1.0)	20	60	1	26

<sup>a</sup>Analysed by <sup>1</sup>H NMR spectrometry.

The results recorded (**Table 7**) have suggested that as the temperature was raised by 10 °C, the reaction rate was doubled (Entries 1 & 2) and that an increased amount of KOH has also enhanced the rate of the reaction (Entries 3 & 4).

The reduction of the acetophenone (**27**) proceeded in a similar fashion to the oxidation reaction except that IPA was used in place of acetone (**Scheme 57**). The results obtained have been tabulated as shown (**Table 8**).

### Scheme 57



**Table 8.** Rhodium-catalysed reduction of ketone (**27**)

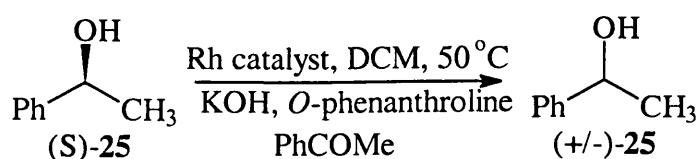
Entry	Catalyst (mol %)	KOH (mol %)	Temp °C	Time (h)	% Conv <sup>a</sup>
1	[Rh(cod)Cl] <sub>2</sub> (2.0)	20	RT	24	25
2	[Rh(cod)Cl] <sub>2</sub> (2.0)	10	60	3	47
3	[Rh(cod)Cl] <sub>2</sub> (2.0)	20	60	3	81
4	Rh <sub>2</sub> (OAc) <sub>4</sub> .2H <sub>2</sub> O (1.0)	10	80	20	22
5	Rh <sub>2</sub> (OAc) <sub>4</sub> .2H <sub>2</sub> O (2.0)	10	80	20	83
6	Rh <sub>2</sub> (OAc) <sub>4</sub> .2H <sub>2</sub> O (2.0)	20	60	1	100
7	[Rh(hd)Cl] <sub>2</sub> (2.0)	10	60	5	72

<sup>a</sup>Analysed by <sup>1</sup>H NMR spectrometry.

The findings from the reduction reactions have provided more information about these catalysts. Out of the three pre-catalysts tested, Rh<sub>2</sub>(OAc)<sub>4</sub>.2H<sub>2</sub>O gave the fastest rate of reaction. As illustrated the reduction reaction catalysed by Rh<sub>2</sub>(OAc)<sub>4</sub>.2H<sub>2</sub>O was complete after 1 hour at 60 °C (Entry 6). The data gathered also indicated a rate enhancement with higher catalyst concentrations used (Entries 4 & 5).

### Racemisation Reactions

To the best of our knowledge, rhodium catalysts have not previously been used for the racemisation of alcohols. Prior to the racemisation procedure, pre-activation of the catalyst was necessary. The pre-treatment process entails a reaction between a pre-catalyst and a ligand in the presence of a base under a nitrogen atmosphere. Once the catalyst had been activated, the alcohol (*S*)-**25** and the acetophenone (**27**) (1 eq) were added (Scheme 58).

**Scheme 58**



**Table 9.** Rhodium-catalysed racemisation of the alcohol (S)-**25**

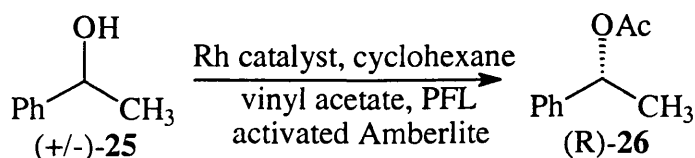
Entry	Catalyst (mol %)	PhCOMe	Time (h)	% Yield	% ee <sup>a</sup>
1	[Rh(cod)Cl] <sub>2</sub> (3.0) <sup>b</sup>	1.0 eq	72	70	39
2	[Rh(cod)Cl] <sub>2</sub> (3.0)	0.1 eq	24	-	63
3	Rh <sub>2</sub> (OAc) <sub>4</sub> .2H <sub>2</sub> O (3.0)	1.0 eq	120	73	1
4	Rh <sub>2</sub> (OAc) <sub>4</sub> .2H <sub>2</sub> O (3.0)	0.5 eq	120	59	3
5	Rh <sub>2</sub> (OAc) <sub>4</sub> .2H <sub>2</sub> O (3.0)	0.35 eq	120	73	1
6	Rh <sub>2</sub> (OAc) <sub>4</sub> .2H <sub>2</sub> O (10.0) <sup>c</sup>	none	20	100	18
7	Rh <sub>2</sub> (CO <sub>2</sub> CF <sub>3</sub> ) <sub>4</sub> (5.0)	0.5 eq	24	-	51

<sup>a</sup> Analysed by chiral HPLC. <sup>b</sup> The reaction was performed at RT. <sup>c</sup> Reaction was performed at 65 °C in hexane and air was removed under vacuum then displaced by N<sub>2</sub>.

All the rhodium catalysts investigated exhibit good rates of racemisation, even when a sub-stoichiometric amount of the acetophenone (**27**) was used (**Table 9**). Rhodium acetate in particular was superior to the other species. Furthermore, the racemisation of the alcohol (S)-**25** by rhodium acetate (10 mol%) in the absence of the acetophenone (**27**) gave 18% ee after 20 hours (Entry 6). Aliphatic secondary alcohols were also examined but slower racemisation rates were observed. The quest to find a suitable rhodium catalyst has used many rhodium cationic species. Despite several attempts these catalysts failed to racemise the alcohol (S)-**25**.

### Dynamic Kinetic Resolution Reactions

The DKR of the alcohol (**25**) was conducted using PFL, vinyl acetate/cyclohexane (2:1) and rhodium catalyst in the presence of a base (**Scheme 59**).

**Scheme 59**

**Table 10.** Rhodium-catalysed racemisation coupled with enzymatic resolution of (25)

Entry	Catalyst (mol %)	Time (h)	Temp °C	% Conv <sup>a</sup>	% ee (R)-26 <sup>b</sup>
1	Rh <sub>2</sub> (OAc) <sub>4</sub> .2H <sub>2</sub> O (2.0)	72	20	60	98
2	Rh <sub>2</sub> (OAc) <sub>4</sub> .2H <sub>2</sub> O (5.0)	120	RT	66	100
3	Rh <sub>2</sub> (OAc) <sub>4</sub> .2H <sub>2</sub> O (20)	120	RT	70	100
4	<b>Rh<sub>2</sub>(OAc)<sub>4</sub>.2H<sub>2</sub>O (20)</b>	<b>144</b>	<b>RT</b>	<b>82</b>	<b>&gt;99</b>
5	[Rh(cod)Cl] <sub>2</sub> (3.0) <sup>c</sup>	144	50	76	80
6	Rh <sub>2</sub> (CO <sub>2</sub> CF <sub>3</sub> ) <sub>4</sub> (10) <sup>d</sup>	288	70	>95	0

<sup>a</sup> Determined using <sup>1</sup>H NMR. <sup>b</sup> Analysed by chiral HPLC. <sup>c</sup> Conducted in DCM, *O*-phenanthroline (6 mol%), PhCOMe (1 eq) and KOH (10 mol%). <sup>d</sup> DCM and K<sub>2</sub>CO<sub>3</sub> (30 mol%) were used.

The results obtained (**Table 10**) have demonstrated >50% conversions to the acetate (**26**) using different rhodium species. Although >95% conversion was achieved using rhodium trifluoroacetate, the acetate product obtained was racemic (Entry 6). Rhodium trifluoroacetate was later found to catalyse the acylation reaction, thus high conversion and no enantioselectivity was observed. Good working DKR reactions were recorded when rhodium acetate was used as the racemisation catalyst. Up to 82% conversion with >99% ee was achieved after 144 hours (Entry 4). <sup>1</sup>H NMR data gave matching peaks with data obtained for the acetate (**26**) already available and the conversions were calculated based on the ratio between the quartet at 5.87 ppm for product (**26**) and a quartet at 4.98 ppm for substrate (**25**). Also the conversions determined by <sup>1</sup>H NMR were similar to the conversions determined by chiral HPLC. Since the alcohol substrate (**25**) and the product (**26**) can be resolved under the same HPLC conditions. Initially it was believed that the boost in the conversion could be due to the loss of alcohol (**25**) by air oxidation. The data gathered, however, from <sup>1</sup>H NMR and chiral HPLC did not shown a large build-up of the acetophenone (**27**) which may have given a false conversion. Other similar DKR results were also

obtained (Entries 1-3) using rhodium acetate. However, because aliquots were removed during the reaction for analysis, the isolated yields were never determined.

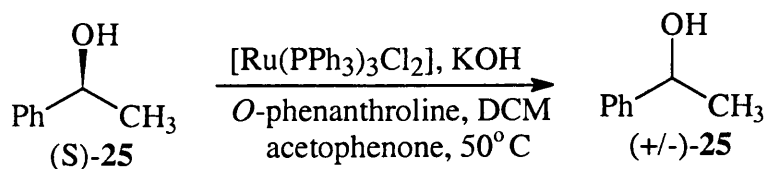
### D.1.8 Ruthenium Catalysts

Ruthenium is a transition metal which lies below iron and next to rhodium in the periodic table. The reactivity of ruthenium is similar to that of rhodium and perhaps ruthenium catalysts are better known<sup>51,62-64</sup> for their transfer hydrogenation capabilities than rhodium catalysts.

### Racemisation Reactions

The racemisation of the alcohol (S)-**25** catalysed by ruthenium catalysts were conducted in a similar way to that of rhodium. Initially  $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2 \cdot \text{H}_2\text{O}$  (3 mol%) was activated with *O*-phenanthroline (5 mol%) in the presence of KOH (20 mol%) at 50 °C in DCM for 15 minutes under an inert atmosphere. This was followed by an addition of the alcohol (S)-**25** and acetophenone (**27**) (Scheme 60). A reduction in the rate of racemisation was observed when a sub-stoichiometric amount of the acetophenone (**27**) was used (Table 11).

Scheme 60

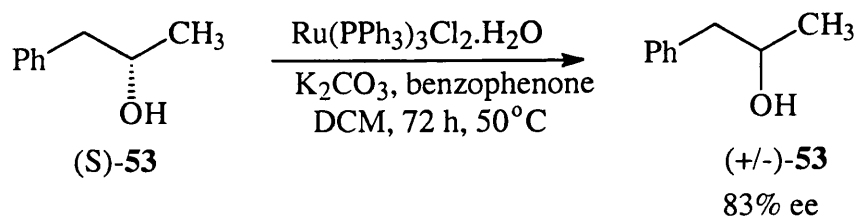


**Table 11.** Ruthenium-catalysed racemisation of the alcohol (S)-**25**

Entry	PhCOMe	Time (h)	% Yield <sup>a</sup>	% ee (S)- <b>25</b> <sup>b</sup>
1	1.0 eq	48	71	51
2	0.5 eq	96	70	58
3	0.35 eq	96	81	76
4	0.5 eq <sup>c</sup>	72	-	48
5	0.5 eq <sup>d</sup>	72	-	48

<sup>a</sup> Isolated yield. <sup>b</sup> Analysed using chiral HPLC. <sup>c</sup> Operate at 70 °C with K<sub>2</sub>CO<sub>3</sub> (20 mol%) in cyclohexane without ligands. <sup>d</sup> Reaction was run at 70 °C using Ru(bipy)<sub>2</sub>Cl<sub>2</sub>.H<sub>2</sub>O (5 mol%) and K<sub>2</sub>CO<sub>3</sub> (20 mol%) in cyclohexane and without ligands.

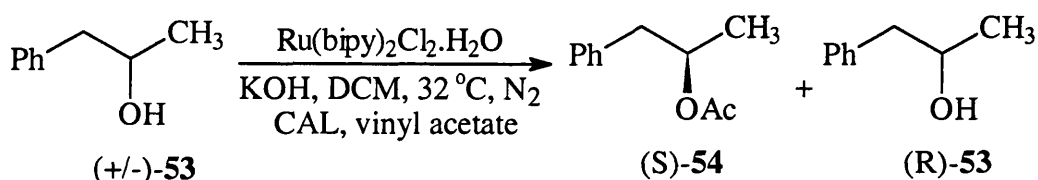
The pre-catalysts can be used for the racemisation of the alcohol (S)-**25** directly without activation and after 72 hours the 48% ee was observed (Entries 4 & 5). The racemisation of the aliphatic alcohol (S)-**53** was also observed using ruthenium pre-catalyst (5 mol%), benzophenone (0.5 eq) and K<sub>2</sub>CO<sub>3</sub> (30 mol%). The reaction was stopped after 72 hours and (S)-**53** was recovered in 83% ee (Scheme 61).

**Scheme 61****Dynamic Kinetic Resolution Reactions**

The DKR studies of the alcohol (**25**) at best gave 60% conversions with 62% ee. The DKR of the alcohol (**53**) (Scheme 62), however, gave 69% conversion with 73% ee of (R)-**54** (Table 12). As indicated by <sup>1</sup>H NMR spectroscopy, unknown impurities as well as the corresponding peaks for the acetate (**54**) and the alcohol (**53**) were observed and this may have interfered with the determination of the results. The enantiomeric excess of the acetate (**54**) was determined by chiral HPLC (and by co-

injecting the racemic sample) using Chiralcel OD column, 99:1 (Hex/IPA),  $\lambda = 254$  nm, 1 mL/min,  $R_t$  (S)-**54** = 4.9 min and  $R_t$  (R)-**54** = 6.5 min. The absolute configuration of the acetate (R)-**54** was determined by the depletion of the alcohol (R)-**53** ( $R_t$  = 15.0 min under the same HPLC conditions).

#### Scheme 62



**Table 12.** A DKR of the aliphatic alcohol (**53**)

Time (days)	% Conv <sup>a</sup>	% ee (S)- <b>54</b> <sup>b</sup>	% ee (R)- <b>53</b> <sup>b</sup>
3	50	76	89
5	59	-	100
6	69	73	>99

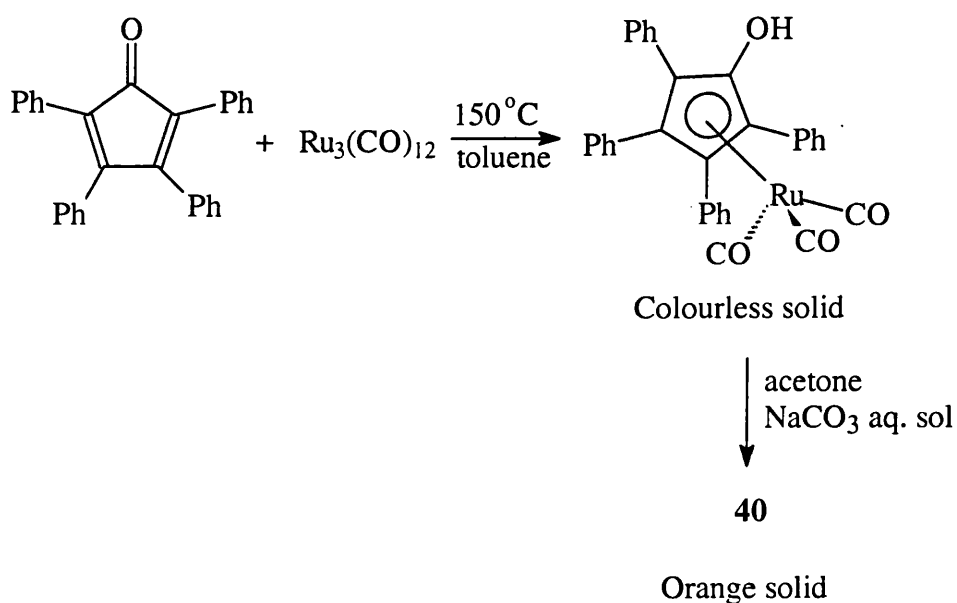
<sup>a</sup> Determined by <sup>1</sup>H NMR. <sup>b</sup> Determined by chiral HPLC.

#### Attempted Preparation of the Ruthenium Dimer (**40**)

Bäckvall and co-workers have demonstrated an efficient ruthenium catalyst (**40**) that is highly active and no base was required. The ruthenium dimer (**40**) was an attractive complex that could form a partnership with an enzymatic resolution reaction without contention. The catalyst (**40**) was prepared by heating Ru<sub>3</sub>(CO)<sub>12</sub> and tetraphenyl cyclopentadienone (4 eq) in a stainless steel reactor for 24 hours. After which, the contents were allowed to cool, purged with nitrogen gas to remove dissolved CO gas and the reaction mixture was re-heated at 150 °C for a further 5 hours. Once cooled, the residue was dissolved in DCM and filtered through a pre-packed column of silica to remove any remaining starting material. The colourless solid [(tetraphenyl cyclopentadienone) tricarbonyl ruthenium (0)] (**Scheme 63**) was collected in only

20% yield. The colourless intermediate obtained was then stirred in acetone and saturated sodium carbonate solution for 30 minutes at room temperature. When an orange solution was formed, it was neutralised and extracted. The solids collected were analysed using  $^1\text{H}$  NMR but there was no evidence (characteristic peak at - 17.75 ppm for Ru-H-Ru) to prove that the catalyst (**40**) had been formed.

#### Scheme 63



Since Bäckvall and co-workers<sup>76</sup> have also accomplished the DKR of the alcohol (**25**) using the catalyst (**40**), Novozym 435 and an aryl acetate to give 92% isolated yield of the acetate (R)-**26** in >99% ee, the preparation of the catalyst (**40**) was abandoned.

#### D.1.9 Iridium Catalysts

Iridium catalysts have been reported<sup>77-82</sup> to catalyse hydrogen transfer reactions. Most of the work described required enantiomerically pure ligands to manipulate

asymmetric reduction of ketones and imines. Here we hoped to expand the chemistry of iridium catalysts by utilising their capabilities to racemise secondary alcohols.

### Racemisation Reactions

Before the racemisation process could take place, the catalyst must be activated. This was carried out by refluxing  $[\text{Ir}(\text{coe})_2\text{Cl}]_2$  (3 mol%), *O*-phenanthroline ligand (5 mol%) and KOH (20 mol%) in DCM for 10 minutes under an inert atmosphere, this was then followed by the addition of the acetophenone (**27**) and (*R*)-**25** at 50 °C (Scheme 64).

Scheme 64

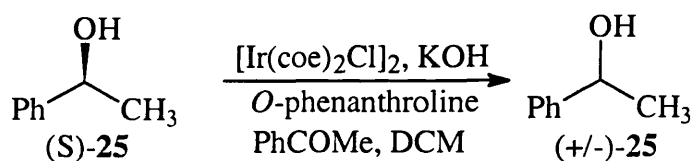


Table 13. Iridium-catalysed racemisation of the enantiomerically pure alcohol (**25**)

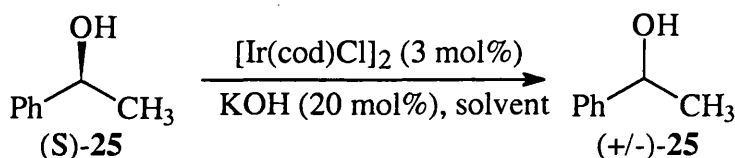
Entry	PhCOMe	Time (h)	Temp °C	% Yield	% ee <sup>a</sup>
1	1.0 eq	24	50	70	8
2	0.45 eq	72	50	63	11
3	0.3 eq	72	50	63	39
4	0.6 eq	24	50	59	43
5	1.0 eq <sup>b</sup>	48	80	-	20

<sup>a</sup> Determined by chiral HPLC using Chiralcel OD column, 99:1 (Hex/IPA),  $\lambda = 254$  nm, 1 mL/min,  $R_t = 18$  min and 24 min. <sup>b</sup> (*R*)-**26** and cyclohexane were used.

Iridium-catalysed racemisation of the alcohol (*S*)-**25** was highly effective, even when a sub-stoichiometric amount of the acetophenone (**27**) was used (Table 13). However, the racemisation processes consist of a variety of reagents and this complexity has made the DKR complicated. To simplify the process some of the

unnecessary additives have to be removed. These include ligands, base and the oxidant (ketone). The simplified conditions will reduce the interference associated with enzymatic resolution coupled with *in situ* racemisation reaction. Successful racemisation attempts of the alcohol (S)-**25** were achieved, even when *O*-phenanthroline ligand and the acetophenone (**27**) were excluded (Scheme 65). A good racemisation rate was still observed even at room temperature to give 13% ee of the alcohol (S)-**25** after 46 hours (Table 14).

**Scheme 65**



**Table 14.** Racemisation of (S)-**25** using iridium catalyst without ligands or ketone.

Entry	Solvent	Temp °C	Time (h)	% Yield	% ee <sup>a</sup>
1	hexane <sup>b</sup>	RT	46	80	13
2	DCM <sup>c</sup>	50	72	-	28
3	DCM	60	48	94	48
4	DCM	RT	22	97	58
5	hexane	RT	48	92	87

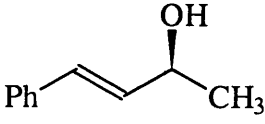
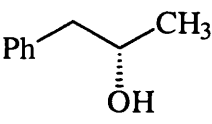
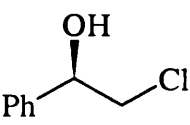
<sup>a</sup> Determined by chiral HPLC. <sup>b</sup> All the solvent was evaporated off overnight, so more was added. <sup>c</sup> PhCOMe (1 eq) was used.

The choice of solvent was important, since no racemisation was observed when ethyl acetate, *t*-butanol, water or acetone were used. Both DCM and hexane exhibited a consistent rate of racemisation. A lot of time was spent on the optimisation of the racemisation reaction promoted by iridium. Despite repeated attempts to replace KOH with a weaker organic base such as triethylamine, KOH was irreplaceable. Also the use of triphenylphosphine ligands did not affect the rate of racemisation. So far



the optimisation investigation has reduced both a number of additives and the complexity associated with the racemisation reactions, but the process is still far from perfect. Overall we have demonstrated the racemisation of other secondary alcohols using iridium catalysts (**Table 15**).

**Table 15.** Iridium-catalysed racemisation of secondary alcohols<sup>a</sup>

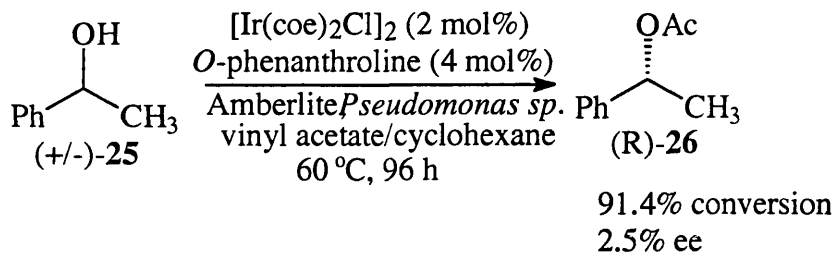
Entry	Substrate	Ketone	Solvent	Temp °C	Time (h)	% ee <sup>b</sup>
1	 55	0.5 eq <sup>c</sup>	DCM	50	70	46
2	 53	none	DCM	RT	48	38
3	 57	none	IPA & acetone	50	36	92

<sup>a</sup> Reactions were performed using [Ir(cod)Cl]<sub>2</sub> (3 mol%), KOH (20 mol%) and *O*-phenanthroline ligand (5 mol%), except entry 1. <sup>b</sup> Analysed by chiral HPLC. <sup>c</sup> Reaction was conducted without ligand, and the corresponding ketone and [Ir(coe)<sub>2</sub>Cl]<sub>2</sub> were used.

### Dynamic Kinetic Resolution Reactions

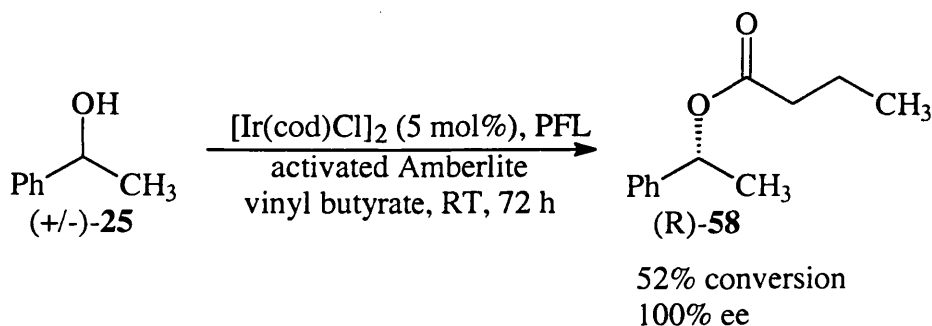
The attempted DKR of the alcohol (**25**) was achieved in 91% conversion, although the acetate product (**26**) was obtained with only 3% ee (**Scheme 66**). Later it was discovered that iridium also catalyses the chemical acylation reaction (76% conversion after 96 hours).

### Scheme 66



A DKR was repeated (Scheme 67) using vinyl butyrate as an acyl donor and immobilised PFL.

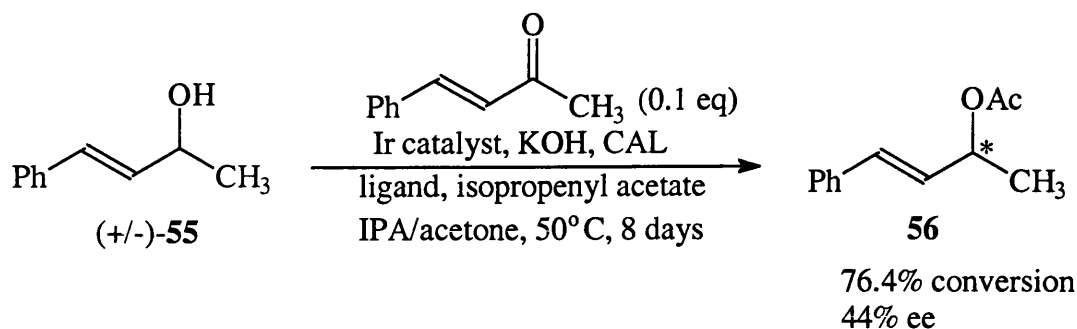
### Scheme 67



A 52% conversion in 100% ee does not represent a working DKR reaction. Nevertheless, the results obtained have illustrated that no chemical acylation was occurring during the process, hence high enantioselectivity was observed. The identity of the product was determined by  $^1\text{H}$  NMR, IR and chiral HPLC. All the data compiled corresponded to the butyrate product (58).

The DKR of the allylic alcohol (55) was also examined. In this case immobilised lipase from *Candida antarctica* and isopropenyl acetate were used in the presence of  $[\text{Ir}(\text{cod})\text{Cl}]_2$  (3 mol%), KOH (20 mol%) and the corresponding ketone (0.1 eq) (Scheme 68). After 8 days the acetate (56) was obtained in 76% conversion with 44% ee (analysed by  $^1\text{H}$  NMR and chiral HPLC).

## Scheme 68

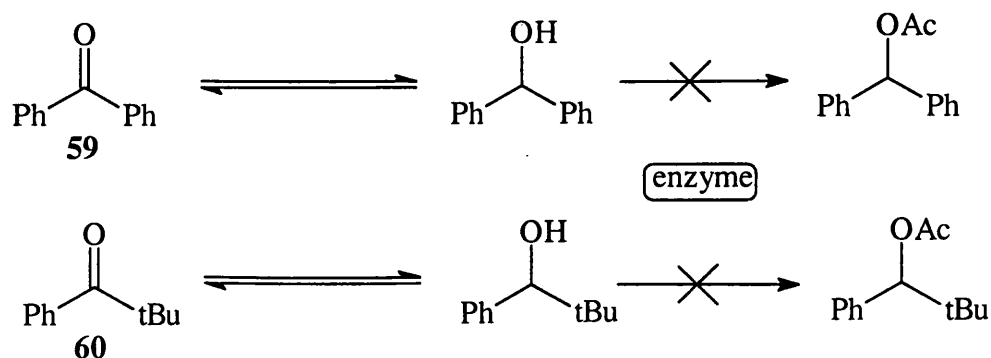


Ideally we would expect to achieve enantiomerically pure (**56**). The DKR was often interfered by the competing chemical acylation reaction caused by the racemising catalysts, therefore a 44% ee of (**56**) was the best result observed.

## D.2.0 Universal Ketones

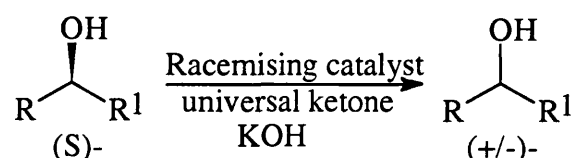
The role of a ketone in the racemisation process is important. The presence of a ketone increases the rate of racemisation because they readily receive a hydride in the transfer hydrogenation process. Ketones such as benzophenone (**59**) and 2,2-dimethyl propiophenone (**60**) were used as universal ketones. These ketones when temporarily reduced to their alcohols do not become acylated (Scheme 69) by an enzyme due to their bulkiness.

## Scheme 69



The introduction of a universal ketone has facilitated the racemisation of different alcohols. A summary of all the results obtained are shown below (**Table 16**). Although the racemisation of these alcohols took place, the rate of racemisation was comparatively slower than the racemisation reactions containing the corresponding ketones (**Scheme 70**). Yet, the alcohol (**(S)**-**25**) was completely racemised when iridium and aluminium catalyst were used (Entries 1 & 2).

**Scheme 70**



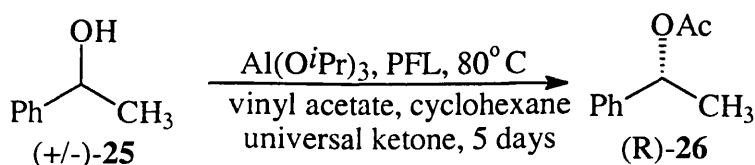
**Table 16.** Racemisation of secondary alcohols using universal ketone (**59**)

Entry	Alcohol	Catalyst (mol %)	Temp °C	Time (h)	% ee <sup>a</sup>
1	( <b>S</b> )- <b>25</b>	[Ir(coe) <sub>2</sub> Cl] <sub>2</sub> ( <b>3</b> )	80	5	1
2	( <b>S</b> )- <b>25</b>	Al(O <sup><i>i</i></sup> Pr) <sub>3</sub> ( <b>20</b> ) <sup>b</sup>	80	144	4
3	( <b>S</b> )- <b>25</b>	Rh <sub>2</sub> (CO <sub>2</sub> CF <sub>3</sub> ) <sub>4</sub> ( <b>5</b> )	70	24	51
4	( <b>S</b> )- <b>53</b>	[Ir(coe) <sub>2</sub> Cl] <sub>2</sub> ( <b>3</b> )	70	72	69
5	( <b>S</b> )- <b>55</b>	[Ir(coe) <sub>2</sub> Cl] <sub>2</sub> ( <b>3</b> )	50	70	46
6	( <b>S</b> )- <b>55</b>	Rh <sub>2</sub> (OAc) <sub>4</sub> .2H <sub>2</sub> O ( <b>6</b> )	50	55	61

<sup>a</sup> Determined by chiral HPLC. <sup>b</sup> No base was used.

The DKR reactions utilising the universal ketone (**59**) and (**60**) were studied using the alcohol (**25**). After 5 days (**Scheme 71**), the acetate product (**(R)**-**26**) was obtained in 73% conversion with 17-20% ee for both cases (**Table 17**). The corresponding alcohols of (**59**) and (**60**) did not transform into their acetates as shown by <sup>1</sup>H NMR.

**Scheme 71**



**Table 17.** Attempted DKR using universal ketones

Entry	Ketone (1 eq)	% Conversion <sup>a</sup>	% ee (R)-26 <sup>b</sup>
1	59	73	20
2	60	73	17

<sup>a</sup>Determined by <sup>1</sup>H NMR. <sup>b</sup>Analysed using chiral HPLC.

### D.2.1 Summary

Enzymatic resolution reactions have played a vital part in organic chemistry for the preparation of enantiomerically pure compounds. The work carried out has stretched enzymatic resolutions to their limit. So far we have demonstrated that secondary alcohols can be racemised under transfer hydrogenation pathways and by MPVO routes. We have demonstrated that a universal ketone can replace the acetophenone (27) while maintaining a good reaction rate for the racemisation of the alcohol (S)-25. The DKR of secondary alcohols represents a powerful technique in enzyme chemistry and 76-82% conversion with 80->99% ee of (R)-26 has been achieved.<sup>96</sup> The developments in DKR have been expanding rapidly over the years and a perfect DKR<sup>97</sup> would be of great significance.

## **Chapter 3**

## E.1.0 $\alpha$ -AlkylAryl Esters

### E.1.1 Introduction

The carboxyl functionality has been the stepping stone for many chemical and biochemical transformations. The carboxyl group is one of the most widely occurring functionalities in chemistry. Carboxyl compounds react readily in water and undergo transesterification reactions, or nucleophilic addition *via* the enolate.

Biologically,  $\alpha$ -alkylaryl acids are an important class of non-steroidal anti-inflammatory compounds. Like other drugs each enantiomer has a different biological activity, so enantiomerically pure  $\alpha$ -alkylaryl acids are extremely valuable. A single enantiomer of a racemic mixture can be extracted by enzymatic resolution reactions. Enzymatic resolution reactions, however, only give 50% of the desired product based on the racemate and chemical resolution reactions on the other hand are expensive and labour intensive.

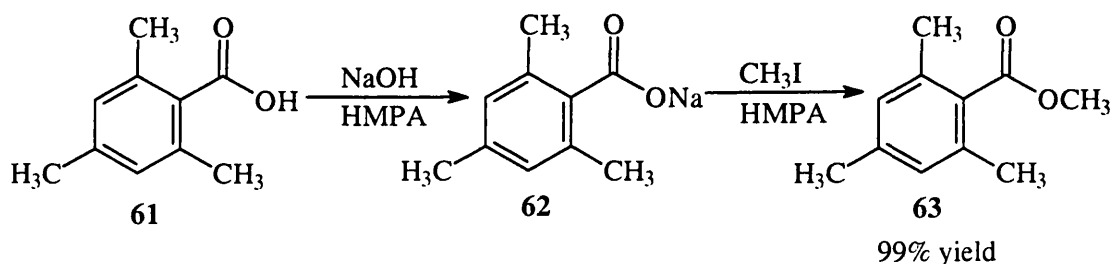
Even now organic chemists are still searching to find a facile and inexpensive route to synthesise enantiomerically pure  $\alpha$ -substituted esters with high yields. Recently, the preparation of enantiomerically pure amino acids and esters using achiral reagents became possible,<sup>98</sup> but an enantiomerically pure substrate derivative was required. The concept was based on the memory of chirality, which is a new principle in enolate chemistry. Similarly, enantiomerically pure amides induced bond rotation restrictions have also been described as a powerful controller of stereoselectivity.<sup>99</sup> These new strategies combine with other developments using enzyme technologies to

become a powerful force for the preparation of enantiomerically pure esters and amino acids.

### E.1.2 Preparation of Alkyl Esters

The esterification of carboxylic acids has been well established. In the early 1970's, the carboxylic acid (**61**) was converted into the corresponding ester (**63**) in quantitative yield. This was achieved by reaction of the sodium salt (**62**) with methyl iodide in hexamethylphosphoramide (HMPA) at room temperature (**Scheme 72**).<sup>100</sup> This was a simple and speedy method for the preparation of methyl esters. The time required for a complete esterification reaction varied depending on the carboxylic acid and the alkyl halide used with tertiary halides failing to give esters in high yield.

**Scheme 72**

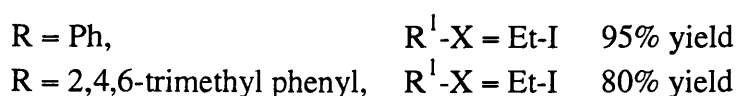
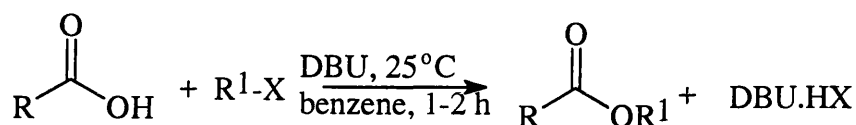


The reaction of an alkyl halide with a tetrabutylammonium (TBA) salt has been used as an efficient method for the synthesis of esters.<sup>101</sup> When DCM was used, the formation of the methylene diester was observed as the by-product, obviously formed by reaction with DCM. The generation of esters from carboxylic acids can be facilitated by a convenient procedure described by Ono and co-workers.<sup>102</sup> The method developed was based on the reaction of carboxylic acids with an alkyl halide in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The reaction proceeded efficiently in a non-polar solvent under mild reaction conditions to give alkyl esters in good yields (**Scheme 73**). This method can be used for sterically



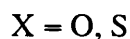
hindered acids, thermally unstable acids and *N*-protected amino acids. Reactions with *N*-protected acids were noticeably smooth to give the corresponding esters without racemisation.

### Scheme 73



Dicyclohexylcarbodiimide (DCC) coupling methods<sup>103</sup> offer rapid reaction rates, high yields and mild reaction conditions for the preparation of esters. It was found that when 3-10 mol% DMAP was used to activate the carboxylic acid, the rate of reaction was accelerated and side reactions were suppressed. The DCC coupling method has lead to a more convenient and efficient synthesis of esters and thioesters than other conventional procedures (Scheme 74).

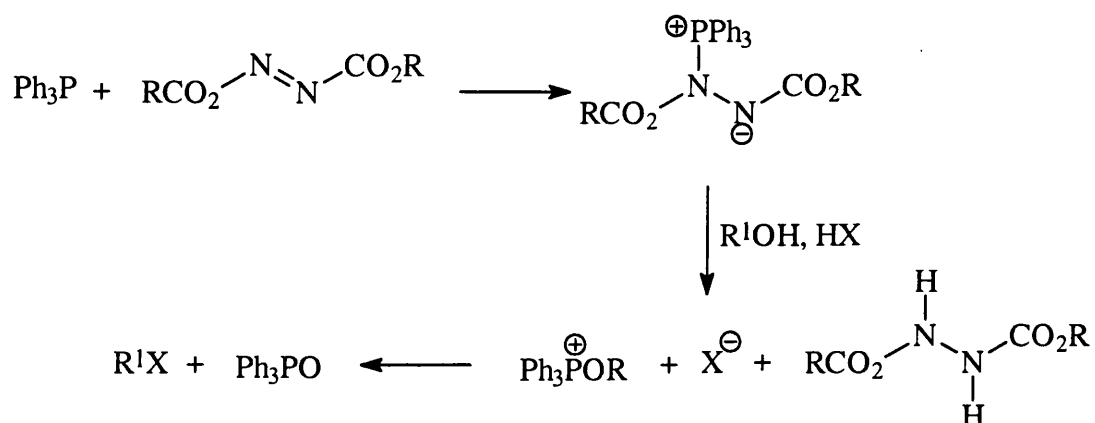
### Scheme 74



The flaw in DCC coupling reactions is a significant side reaction forming the undesired *N*-acylurea by-product. This can be reduced, however, by using solvents such as DCM.<sup>104</sup> For an overall report, Kielbasinski and Milkolajczyk<sup>105</sup> have reviewed the developments in carbodiimide chemistry.

The Mitsunobu reaction<sup>106a-b</sup> is one of the most commonly known reactions for inversion of configuration. Mitsunobu reagents consist of a combination of triphenylphosphine (PPh<sub>3</sub>), diethyl azodicarboxylate (DEAD), an alcohol and an acidic species HX (Scheme 75). The method can be applied to a wide range of functional groups and can be used to prepare esters as long as the pK<sub>a</sub> of HX is less than 13.

**Scheme 75**



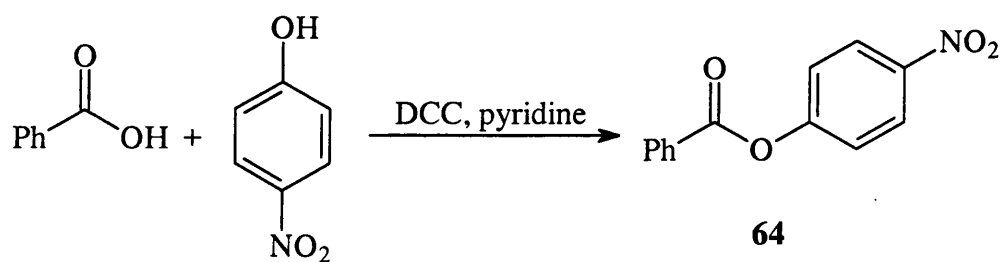
The synthesis of esters using  $\alpha$ -chymotrypsin in high ethanol concentrations has also has been shown.<sup>107</sup> Other procedures to prepare esters and protect carboxyl groups can be seen in a review by Haslam.<sup>108</sup>

### E.1.3 Preparation of Aryl Esters

Aromatic alcohols are poor nucleophiles because of their electron withdrawing properties. Consequently, the preparation of aryl esters is difficult and the yields are usually low. Phenolic esters can be prepared by condensing an acid chloride with a phenolic alcohol in the presence of aqueous alkali or pyridine. The preparation of acid chlorides involve the use of thionyl chloride, oxalyl chloride or phosphorus

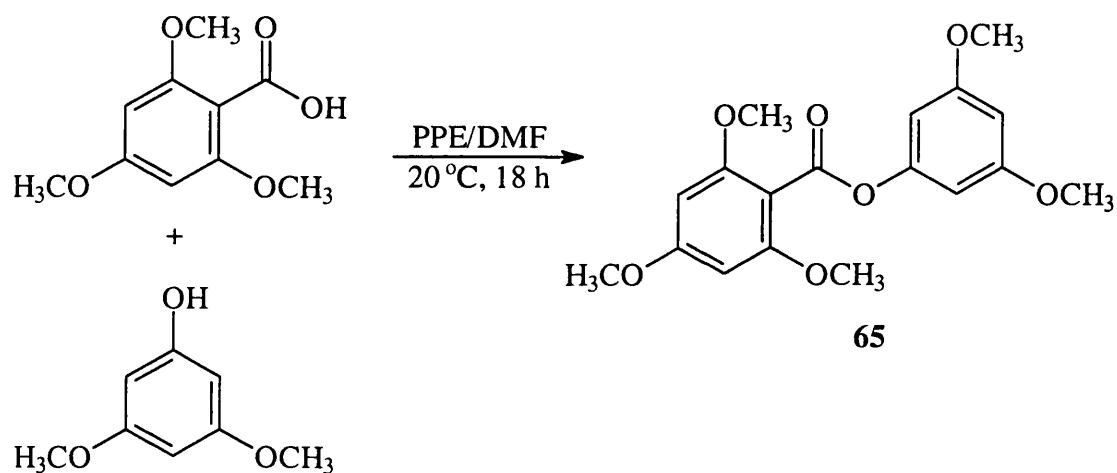
pentachloride which forms hydrogen chloride as by-product which is difficult to remove. The preparation of *p*-nitrophenol benzoate (**64**) using a DCC coupling procedure gave good yields<sup>109</sup> (**Scheme 76**) and the purification process was simple since the urea by-product is insoluble in most solvents.

**Scheme 76**



The preparation of aryl esters using polyphosphate ester (PPE) in dimethylformamide (DMF) has been documented (**Scheme 77**). Compared with other procedures, the method using PPE is relatively inexpensive and PPE can be easily prepared. The synthesis of the ester (**65**) using PPE at room temperature gave 93% yield after 18 hours.<sup>110</sup>

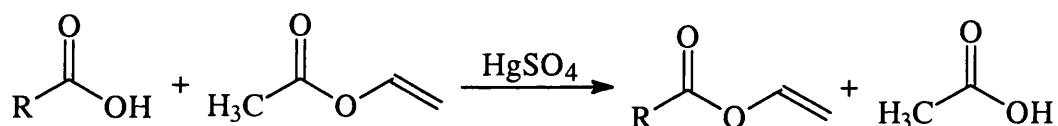
**Scheme 77**



#### E.1.4 Preparation of Vinyl Esters

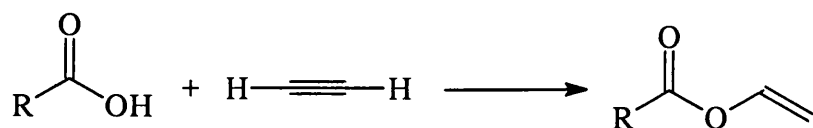
Vinyl esters are more difficult to prepare than alkyl or aryl esters. The synthesis of vinyl esters does not proceed under acid or base catalysed conditions. Usually the commonly used method for the preparation of vinyl esters is the vinyl interchange reaction. This is the reaction between vinyl acetate and carboxylic acids and is catalysed by mercuric salts such as mercuric sulfate ( $\text{HgSO}_4$ ).<sup>111</sup> A general reaction scheme for the vinyl interchange process is shown below (**Scheme 78**).

**Scheme 78**



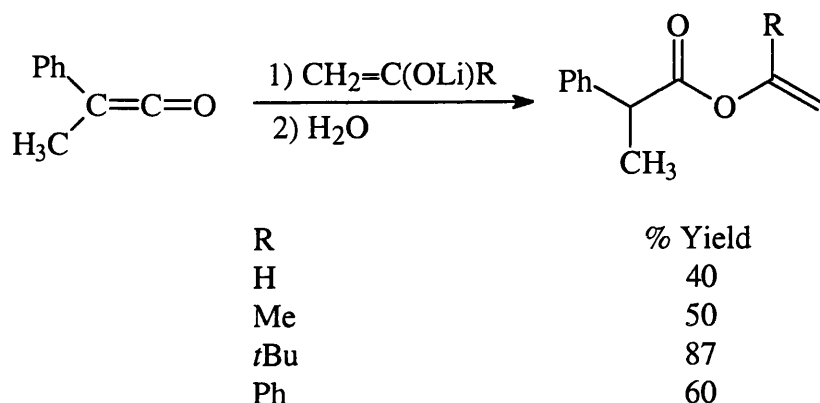
The reaction conditions for the vinyl interchange reaction is mild and the vinyl ester products can be obtained in high yields with low impurities. Compared with the acetylene route (**Scheme 79**), the vinyl interchange reaction offers a facile and a more reliable route to the preparation of vinyl esters.

**Scheme 79**



The generation of lithium enolates and subsequent *O*-acylation reaction with ketenes has also created an efficient method to the preparation of vinyl esters (**Scheme 80**). Reactions with potassium enolates, however, generated from ketones by potassium hydride (KH) in THF gave only *C*-acylation products. Thus the choice of lithium or potassium enolates permits the formation of *O*-acylation or *C*-acylation products.<sup>112ab</sup>

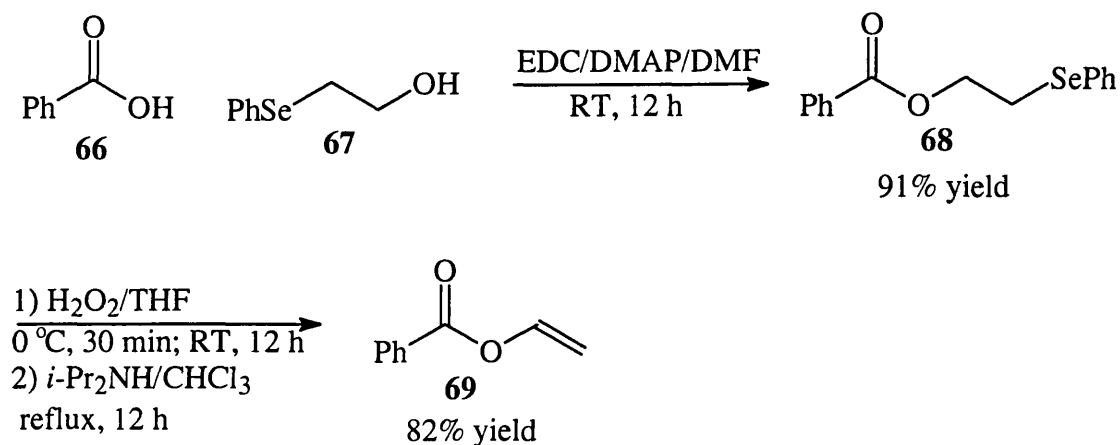
## Scheme 80



Acetaldehyde enolate was generated from THF with *n*-BuLi at 25 °C and other enolates were prepared from their ketones with LDA in THF at -78 °C, or with KH in THF at room temperature.

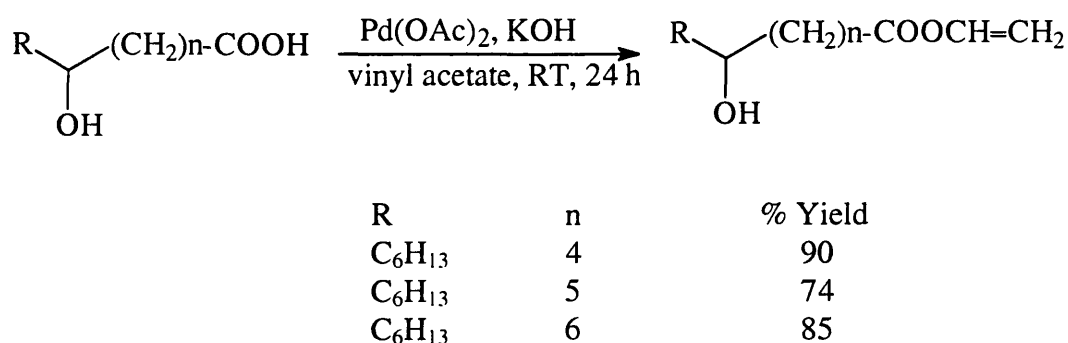
Modern synthetic approaches to the preparation of vinyl esters have engaged organoselenium reagents.<sup>113</sup> Reaction of the benzoic acid (**66**) with 2-(phenylseleno) ethanol (**67**) in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and DMAP gave the selenide (**68**). Oxidation of (**68**) using hydrogen peroxide followed by reflux of the crude mixture in chloroform gave the vinyl ester (**69**) in 82% yield (**Scheme 81**).

### Scheme 81



Schneider and co-workers<sup>114</sup> have recently reported the preparation of vinyl esters using palladium catalysts. The formation of vinyl esters was achieved by reaction of carboxylic acids with vinyl acetate under basic conditions and in the presence of palladium(II) acetate (**Scheme 82**). A detailed research study was carried out and palladium(II) acetate was found superior to  $\text{Li}_2\text{PdCl}_4$  and other palladium species. Also the addition of KOH (10 mol%) and using low reaction temperatures ( $20^\circ\text{C}$ ) have suppressed the side reaction that forms acetyl ester.

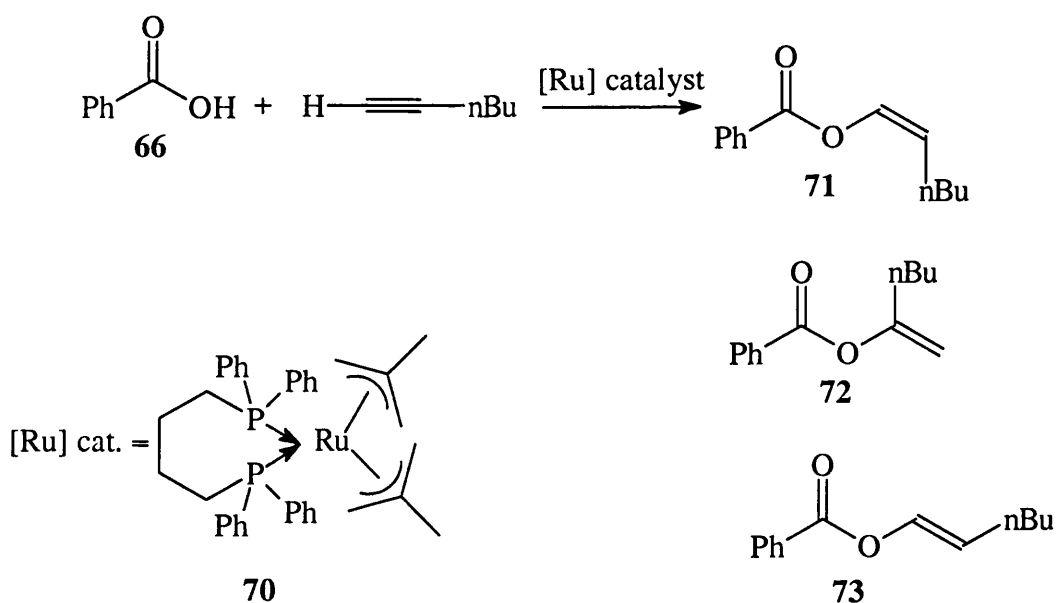
### Scheme 82



Overall, there has been a lack of literature reports for the preparation of vinyl esters and the procedures that are already documented often present problems such as side

reactions, harsh reaction conditions and poor yields. With recent interests in transition metal catalysed reactions, ruthenium-catalysed *trans*-addition of carboxylic acids to terminal alkynes to produce vinyl esters was reported.<sup>115</sup> The regioselectivity for the addition of carboxylic acids to alkyne was dependent on the ruthenium catalyst used. For example the ruthenium catalyst (**70**) gave selectively terminal addition under reaction conditions comprising (**66**) (1 eq), hex-1-yne (1 eq) and the catalyst (**70**) (10 mol%) in toluene at 65 °C under an inert atmosphere to afford the vinyl ester (**71**) in high yield (98%) (**Scheme 83**). The procedure described has been demonstrated to work for most carboxylic acids and alkynes to form the desired vinyl esters in high yield.

**Scheme 83**



## F.1.0 Enzymatic Resolution Reactions

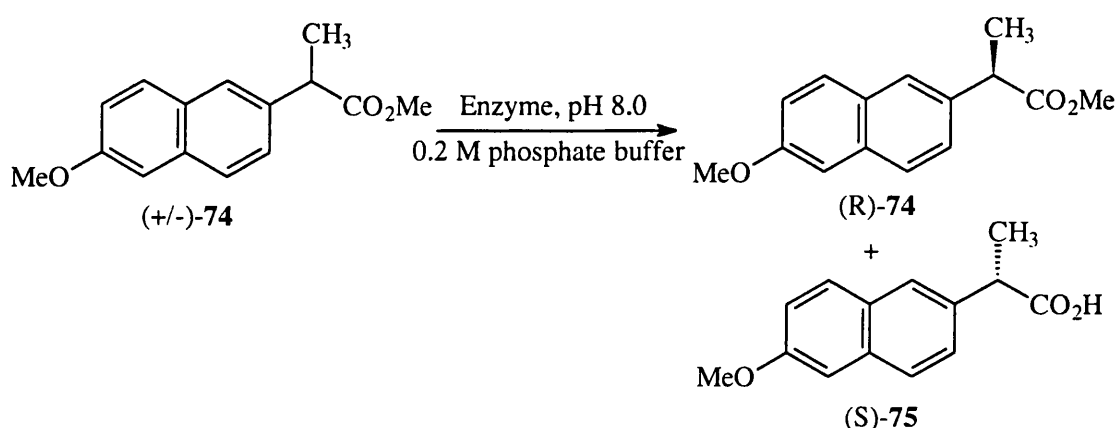
### F.1.1 Enzyme-Catalysed Hydrolysis of Esters

Enantioselective hydrolysis reactions using enzymes have been one of the simplest routes for the resolution of esters, whereas chemical resolution methods have proved

to be expensive and inefficient. Enzyme-catalysed enantio- and regioselective monohydrolysis of diesters have been successfully achieved<sup>116a-c</sup> and these enantiomerically pure monoesters have been used for the preparation of enantiomerically pure compounds.

2-Arylpropionic acids are an important class of non-steroidal anti-inflammatory drugs. These anti-inflammatory drugs often associate high activity with a single enantiomer while the other enantiomer could be inactive. Enzymatic hydrolysis of 2-arylpropionic esters to give enantiomerically pure acids has been successfully achieved.<sup>117</sup> For example the racemic methyl-2-(6-methoxy-2-naphthyl)propionate (**74**) was hydrolysed using lipases derived from the genera *Rhizopus*, *Mucor* and *Candida* to give (**75**) in reasonable yields (**Scheme 84**). The data obtained (**Table 18**) have illustrated that lipase from *Candida cylindracea* gave selectively the (S)-enantiomer, whereas all other lipases gave the (R)-enantiomer.

**Scheme 84**

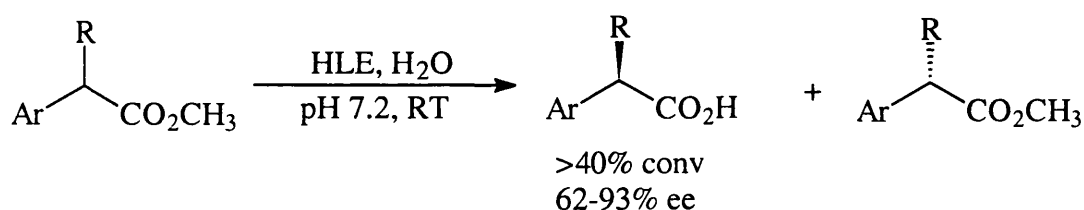




**Table 18.** Enzymatic hydrolysis of methyl ester (74)

Lipase	Stereo-Configuration	% Conv	% ee (74)	% ee (75)	Enantiomeric ratio (E)
<i>Candida cylindracea</i>	S	39	63	>998	>100
<i>Mucor meichei</i>	R	18	21	95	51
<i>Rhizopus arrhizus</i>	R	11	13	97	78
<i>Rhizopus sp.</i>	R	19	21	92	27
<i>Rhizopus oryzae</i>	R	11	10	76	8

Block and co-workers<sup>118</sup> have carried out the hydrolysis of simple methyl esters of 2-arylpropionic acids using horse liver esterase (HLE). HLE is inexpensive and can be easily obtained as a crude acetone powder. The hydrolysis of racemic esters of 2-arylpropionic acids was performed using HLE in water, pH 7.2, at room temperature to give the desired acids at >40% conversion with 62-93% ee (**Scheme 85**). On the other hand, pig liver esterase (PLE) hydrolyses esters rapidly but without any enantiomeric discrimination, therefore PLE has been utilised as a simple procedure for the conversion of (S)-esters into (S)-acids.

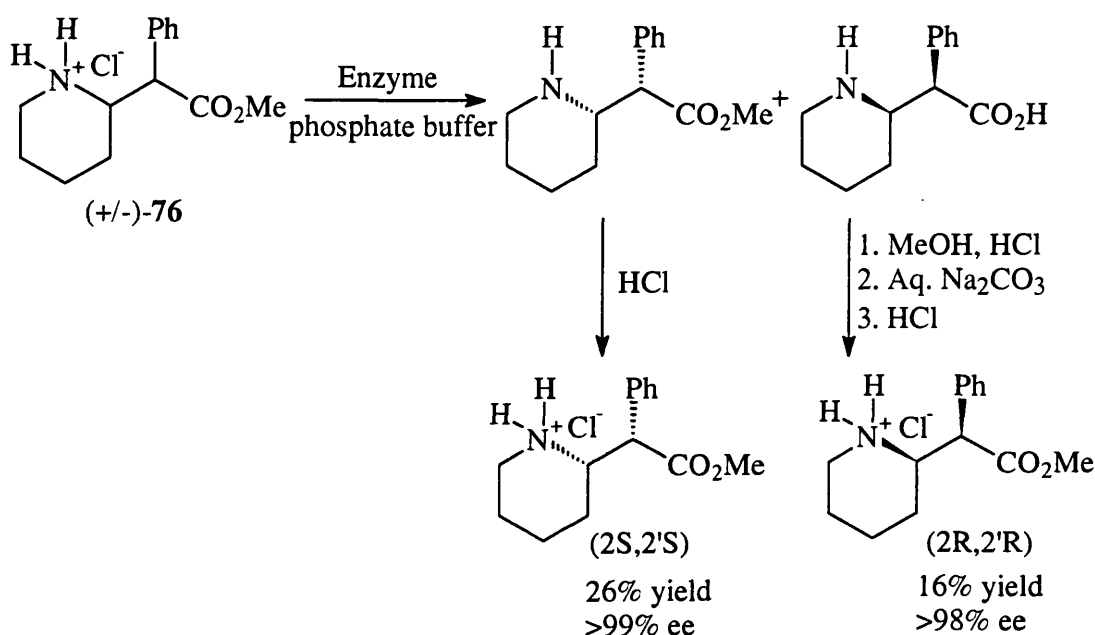
**Scheme 85**

Ar = Ph, MeOph, *p*-*i*BuPh, *p*-ClPh  
 R = Me, Et, *i*Pr

A mild nervous system stimulant (±)-*threo*-methylphenidate hydrochloride (**76**, Ritalin<sup>®</sup> hydrochloride) used for the treatment of children with Attention Deficit Hyperactivity Disorder (ADHD) has been resolved by enzymatic reactions.<sup>119</sup>

(2R,2'R)-(+)-*threo*-(**76**) is more biologically active than the opposite diastereomer and hence the preparation of diastereomerically pure Ritalin is desirable. The hydrolysis of (**76**) was carried out and only  $\alpha$ -chymotrypsin and *Subtilisin carlsberg* exhibited good enantioselectivity but the reaction rates were slow (**Scheme 86**).

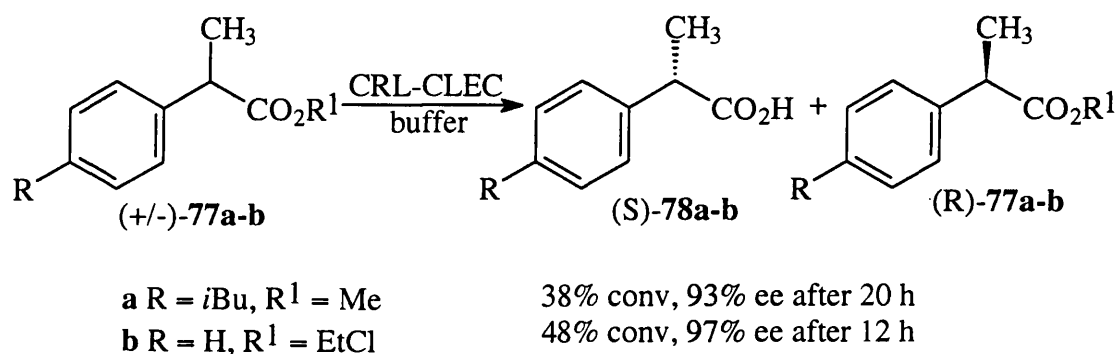
**Scheme 86**



Within the past ten years, the developments in enzyme chemistry have advanced at an incredible rate. Cross-linked enzyme crystals (CLEC) have been marketed by Altus Biologic Inc.<sup>120</sup> and CLEC technology was a success in the 1990's. CLECs were made from crude enzyme crystals that were grown in ammonium sulfate solution and crossed-linked with glutaraldehyde.<sup>121</sup> The catalytic activity of CLEC systems are remarkable. They are highly robust, stable in most solvent systems, withstand extreme pH and high temperatures and they can be reused many times over without any loss of activity.<sup>122a-c</sup> Lipase from *Candida rugosa* (CRL) in the form of CRL-CLEC has been successfully deployed in the enantioselective hydrolysis of the esters of 2-arylpropionic acids. Compared with crude CRL, CRL-CLEC gave higher

enantioselectivity and the rate of hydrolysis was 3-50 times greater. The hydrolysis of (**77a-b**) using CRL-CLEC in buffer gave 93-97% ee to the corresponding carboxylic acids (**78a-b**)<sup>122</sup> (Scheme 87). Under the same reaction conditions, the hydrolysis of (**77a-b**) catalysed by crude CRL gave 82-89% ee.

**Scheme 87**

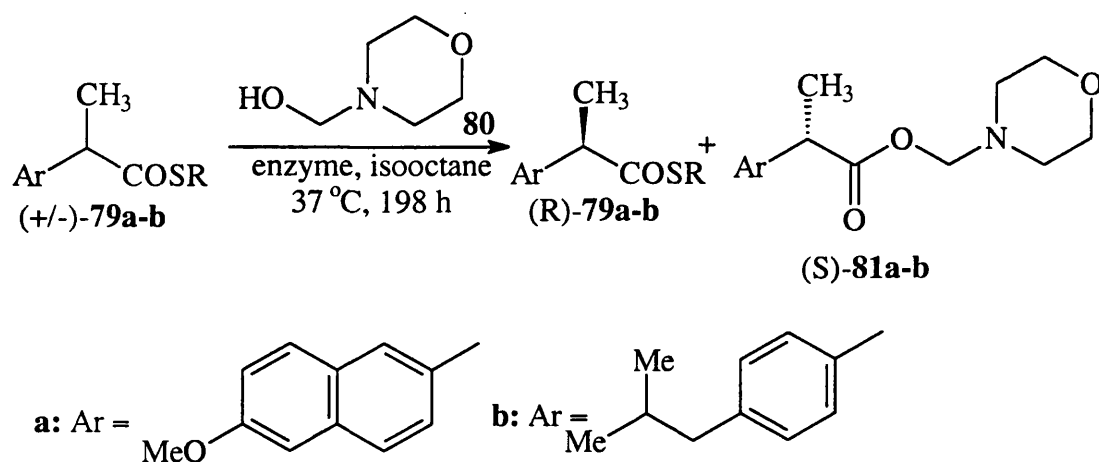


### F.1.2 Enzyme-Catalysed Transesterification Reactions

The resolution of carboxylic acids through enzyme-catalysed transesterification has become an efficient process in organic chemistry. Transesterification reactions have been reviewed by Otera<sup>124</sup> and other reviews on enzyme-catalysed processes have been discussed in chapter 1.<sup>20,23</sup> The introduction of CLEC technologies have led to enzymes becoming more tolerant to extreme conditions such as pH, temperature and solvents.<sup>123,125</sup> Pure enzyme preparations such as CRL-CLEC are more stable in organic solvents and give better reaction rate than the crude CRL.<sup>126</sup> Klibanov and co-workers<sup>127a-c</sup> have studied the effect of solvents in the transesterification reactions. For the transesterification reactions of carboxylates with alcohols, hexane and toluene were found to be effective<sup>128</sup> and solvents such as chloroform, ether, butanol or water-miscible solvents exhibited very little or no reaction at all.

Enantioselective transesterification reactions have been used for the resolution of ( $\pm$ )-sulcatol (insect pheromone)<sup>129</sup> and the resolution of (R,S)-2-arylpropionic acid thioesters to produce (S)-naproxen ester and (S)-ibuprofen has also been cited.<sup>130</sup> The transesterification of the racemic thioesters (**79a-b**) with the alcohol (**80**) in the presence of lipase MY (Meito Sangyo) was achieved to give the corresponding esters (**81a-b**) in high enantiomeric purity. When R = phenyl or trifluoroethyl was used the observed rate of transesterification was increased (**Scheme 88**).

**Scheme 88**



**Table 19.** Lipase MY mediated thiotransesterification of thioesters (**79a-b**)

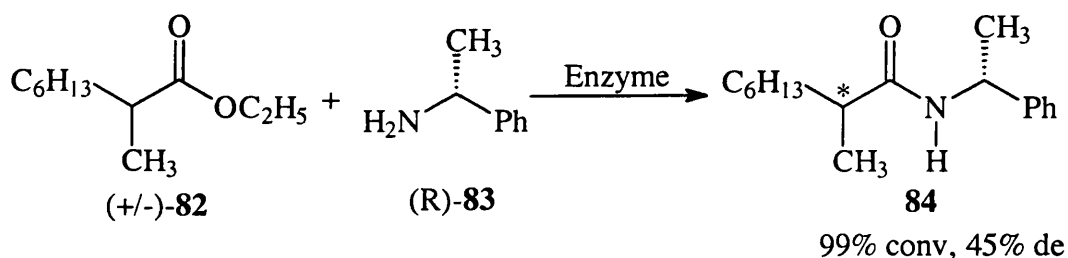
Entry	R	% Conversion	% ee (R)-( <b>79a-b</b> )	% ee (S)-( <b>81a-b</b> )
1	ethyl	2.8	1.9	>99
2	<i>n</i> -propyl	0.6	0.6	>99
3	<i>n</i> -butyl	1.6	1.3	>99
4	phenyl	41.2	64.5	97.8
5	trifluoroethyl	33.4	47.7	91.5

The results obtained (**Table 19**) have suggested that electron-withdrawing groups such as phenyl or trifluoroethyl have enhanced the reaction rate (Entries 4 & 5). Since these electron-withdrawing moieties have caused thioesters to become more

labile, chemical hydrolysis to their carboxylic acids may also take place. Page and co-workers<sup>131</sup> have studied this phenomenon and they have shown that the equilibrium between the hydrolysis and the transesterification reactions were highly dependent on the pKa of the leaving groups and the reaction conditions.

Aminolysis reactions of the racemic ethyl-2-methyloctanoate (**82**) with the enantiomerically pure (R)-1-phenylethylamine (**83**) catalysed by a lipase from *Candida antarctica* at 70 °C (Scheme 89) gave the diastereomeric amide (**84**) at 99% conversion with 45% de after 115 hours.<sup>132</sup>

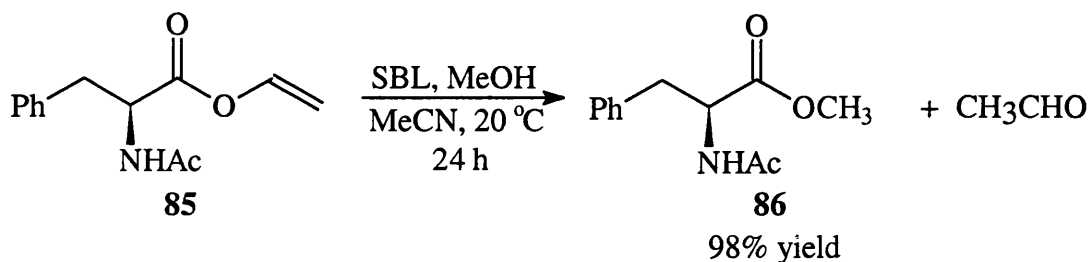
**Scheme 89**



Transesterification reactions can also be carried out in biphasic aqueous-organic mixtures<sup>133</sup> by use of porous supports (Sephacrose or Chromosorb). The procedure developed has enabled the transesterifications to be applied to a wider range of substrates such as water soluble compounds.

The reactions of vinyl esters are irreversible and for this property, vinyl esters have been a popular acyl donating agent. *Subtilisin bacillus lentus* (SBL) catalysed the reaction of *N*-Acetyl-L-phenylamine vinyl ester (**85**) with methanol in acetonitrile to give the ester (**86**) in essentially quantitative yield (Scheme 90). It was found that as the reacting alcohol was increased in size, the rate of reaction was decreased.<sup>134</sup>

## Scheme 90



The procedure described above has demonstrated a useful route to the synthesis of enantiomerically pure esters using enzymes. The main disadvantage of this type of reaction is that hydrolysis will occur in the presence of water, because lipase enzymes can catalyse the hydrolysis reaction under aqueous conditions. The problem, however, can be avoided by using antibody technology.<sup>135</sup>

## G.1.0 Dynamic Kinetic Resolution of Esters

### G.1.1 Introduction

With rapid developments in enzyme chemistry, it is possible to use a racemisation technique with an enzymatic resolution reaction to effect a DKR, as demonstrated by the DKR of secondary alcohols.<sup>97</sup>

Racemisation procedures are often only mentioned very briefly in asymmetric synthesis publications because of problems associated with poor enantiomeric purity.

The racemisation of  $\alpha$ -substituted esters has been limited and very specific. For example mandelate racemase has been used for the racemisation of mandelic acid.<sup>136</sup>

Only very recently Swanenburg and co-workers<sup>137</sup> have extensively reviewed the racemisation of enantiomerically enriched organic compounds including  $\alpha$ -

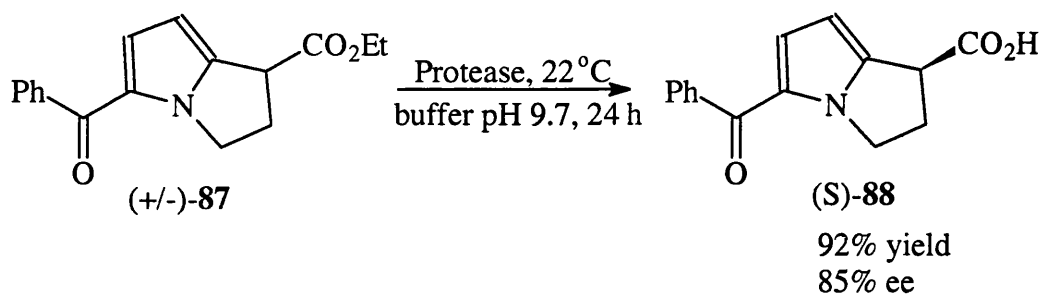
substituted esters. Most of the racemisation procedures described, however, were obtained from patent literature or from industrial establishments.  $\alpha$ -Alkyl carboxylic acids and their derivatives are usually racemised under base or acid catalysis. Often the racemisation of these compounds is performed at very high temperatures, or by treatment with strong bases or acids.

Chemical deracemisation of  $\alpha$ -substituted arylacetic acids<sup>138</sup> and DKR of azlactones using DMAP derivative<sup>139</sup> have been efficient routes for the preparation of enantiomerically pure compounds. Similar work was carried out by Durst and co-workers<sup>140</sup> who have utilised the epimerisation of  $\alpha$ -halo esters for the production of diastereomerically pure  $\alpha$ -amino esters.

### G.1.2 Dynamic Kinetic Resolution Reactions

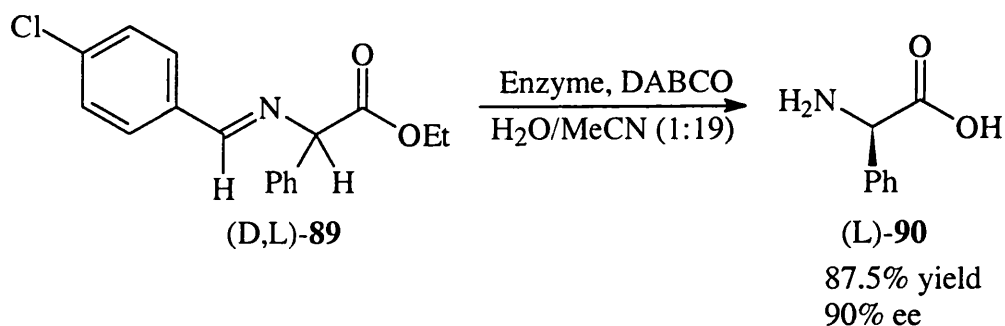
DKR of 2-phenyl-4-alkyl oxazolin-5(4*H*)-ones using a lipase enzyme has been reported.<sup>141</sup> However, reports for the combined base-catalysed racemisation and enzymatic hydrolysis of esters to effect a DKR have been scarce. In 1987 Sih and Fülling<sup>142</sup> conducted an *in situ* racemisation of ketorolac esters under mild basic conditions coupled with an enzymatic hydrolysis reaction. When the racemic (**87**) was suspended in 0.2 M carbonate buffer solution pH 9.7 with *Streptomyces griseus* protease at 22 °C and stirred for 24 hours, the acid product (S)-**88** was obtained in 92% yield and 85% ee (Scheme 91).

### Scheme 91



The hydrolysis of Schiff bases of amino acid esters using  $\alpha$ -chymotrypsin in aqueous-organic solvents combined with *in situ* racemisation reaction using DABCO was reported.<sup>143</sup> It was apparent that the optimum conditions were in aqueous/MeCN (1:19) and DABCO (10 mol%) at ambient temperature. Subsequently the hydrolysis of D,L-**89** in aqueous-organic solvent mix in the presence of DABCO gave L-**90** in 88% yield with 90% ee (Scheme 92).

### Scheme 92



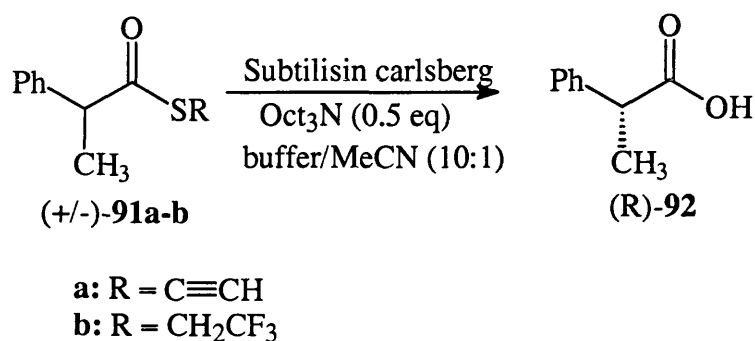
So far, the DKR described have been very specific and the scope for these methodologies are limited. Only very recently, in 1998, the DKR of thioesters was published.<sup>144</sup> The detailed investigation has revealed that the acidity of the  $\alpha$ -protons of different  $\alpha$ -substituted propionate thioesters can be enhanced up to 20-fold by changing the thiol moiety. The hydrolysis of (**91a-b**) under racemisation conditions



(Oct<sub>3</sub>N) with *Subtilisin carlsberg* gave 95-97% conversions and 80-83% ee of (R)-**92**

(Scheme 93).

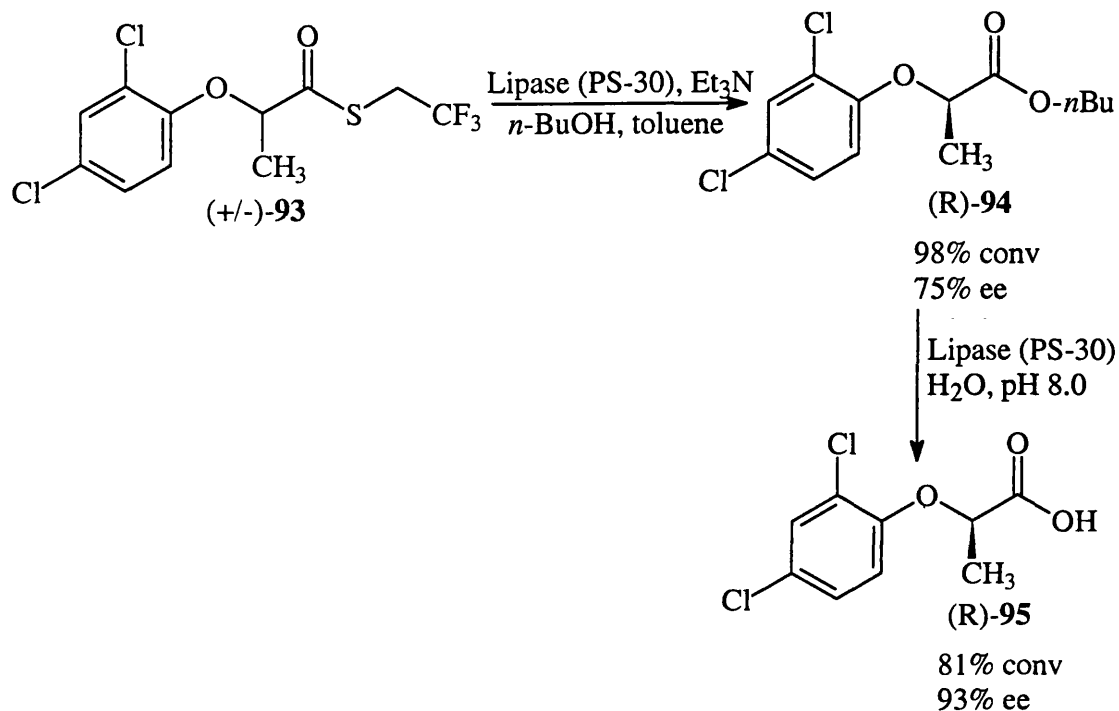
### Scheme 93



The transesterification of the racemic (**93**) with *n*-butanol in the presence of lipase (PS-30), triethylamine and toluene gave (R)-**94** in 98% conversion with 75% ee.

Then a second reaction was performed to hydrolyse (R)-**94** using the same enzyme under aqueous non-racemising conditions to give (R)-**95** in 81% conversion with 93% ee (Scheme 94). These procedures when run consecutively have clearly increased the enantiomeric excess, from 75% to 93%.

Scheme 94



As seen, there are very few examples demonstrating the working DKR of  $\alpha$ -substituted esters. Fewer publications discuss the *in situ* racemisation of  $\alpha$ -substituted esters coupled with enzyme-catalysed resolutions under biphasic conditions. This area of chemistry is still open for further research and perhaps one day a general DKR procedure will be developed. In the mean time the future for DKR of esters remains to be explored.

## **Chapter 4**

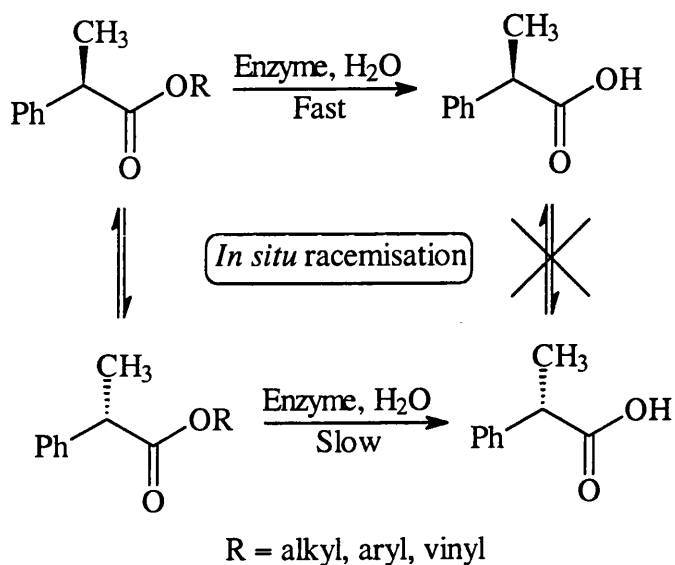
## H.1.0 Results and Discussions

### H.1.1 Aims

$\alpha$ -Substituted acids and their derivatives have been described<sup>117,118,123,143</sup> for the syntheses of amino acids and non-steroidal anti-inflammatory drugs. The limitation for an enzymatic resolution reaction is that only 50% of the product can be obtained. The scope to find an efficient method for the preparation of enantiomerically pure  $\alpha$ -substituted acids and their derivatives by enzymatic resolution methods is enormous.

Our immediate objective was to carry out the racemisation of  $\alpha$ -substituted esters under mild reaction conditions. The racemisation process may involve the use of a transition metal catalyst, or a weak and non-nucleophilic base, or both.  $\alpha$ -Alkylaryl esters tend to racemise more quickly than their corresponding acids. This is because the initial deprotonation of the hydroxyl proton from  $\alpha$ -alkylaryl acids retards the secondary deprotonation at the  $\alpha$ -position. Whereas,  $\alpha$ -alkylaryl esters undergo a single deprotonation at the chiral  $\alpha$ -position to form an  $sp^2$  planar enolate, hence loss of chirality. We believe that the  $\alpha$ -protons of 2-alkyl aryl propionic acids have a higher pKa than the  $\alpha$ -protons of the corresponding esters. The large difference in pKa values between the acids and the esters mean they have a different rate of enolisation (racemisation). This is an important concept for the racemisation of  $\alpha$ -alkylaryl esters. When, and if, the racemisation procedure has been accomplished under mild reaction conditions, our ultimate goal was to couple the racemisation reaction with an enzymatic hydrolysis (**Scheme 95**). In effect we hoped to attain a general DKR procedure for  $\alpha$ -substituted esters.

**Scheme 95**



Above is a schematic representation of the overall aim of the project. There are a few factors that must be considered:-

- 1) The racemisation process must only racemise the starting material (ester) and not the acid product.
- 2) The enzymatic hydrolysis reaction must be highly enantioselective in order to give a good enantiomeric purity of the product.
- 3) The racemisation process must not interfere with the enzyme reaction and chemical hydrolysis of the starting material must not take place.

The success of a DKR of  $\alpha$ -alkylaryl esters will rely on these requirements.

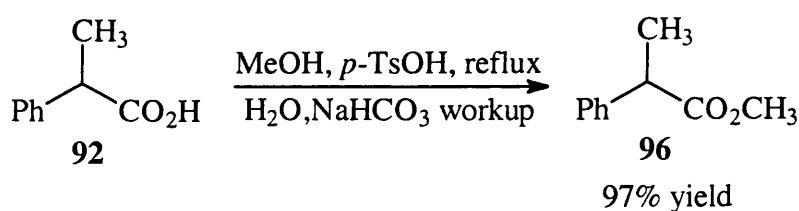
### H.1.2 Racemisation of $\alpha$ -alkylaryl Esters

Initially we had to choose a suitable substrate for the project. The chosen substrate had to be readily available as a racemate and in enantiomerically pure form. In addition, the substrate of choice had to be easily detectable, i.e. a chromophore. In

compliance with these features, we had chosen 2-phenylpropionic acid (**92**) as our starting material.

Methyl-(2-phenyl)propionate (**96**) has been described<sup>118</sup> as a good substrate for enzymatic resolution reactions. The methyl ester (**96**) was not commercially available, so it was prepared through a simple acid catalysed esterification reaction using the starting material (**92**) (Scheme 96). The reaction gave a clean product (pale yellow oil in 97% yield) within 5 hours under reflux in methanol. No racemisation was observed when (S)-**92** was esterified under the same reaction conditions to give enantiomerically pure methyl ester (S)-**96**, also in near quantitative yield.

#### Scheme 96



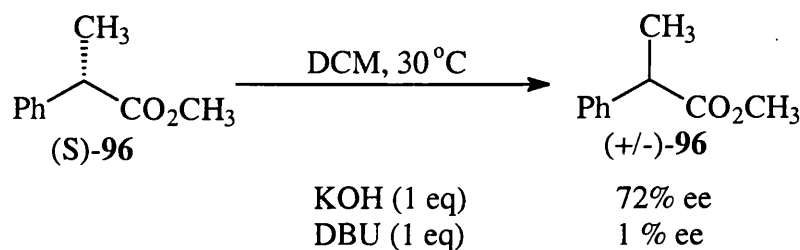
The formation of the methyl ester (**96**) was indicated by the disappearance of an OH peak at 3350 cm<sup>-1</sup> and a shift of a carbonyl peak from 1715 cm<sup>-1</sup> to 1737 cm<sup>-1</sup> (analysed by FT-IR). <sup>1</sup>H NMR analysis gave a extra methyl group indicated by a singlet (integral = 3) at 3.66 ppm.

The racemisation of the methyl ester (S)-**96** was carried out in DCM at 30 °C with a base (Scheme 97). The methyl ester (S)-**96** was recovered in 72% ee under racemisation conditions containing KOH and 1% ee under racemisation conditions containing DBU (determined by chiral HPLC ChiralCel OJ column, 90:10

(Hex/IPA), 1 mL/min,  $\lambda$  = 254 nm, Rt (R)-**96** = 7.5 min & Rt (S)-**96** = 8.6 min).

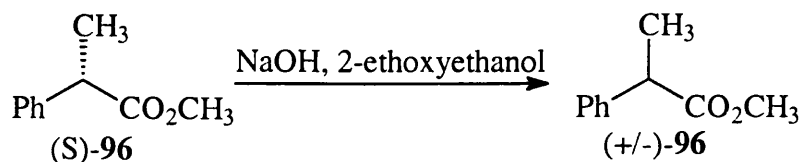
Under racemisation conditions containing DBU (1 eq), the acid (S)-**92** was also racemised down to 80% ee after 20 hours (determined by chiral HPLC ChiralCel OD column, 97.89:2:0.2 (Hex/IPA/HCO<sub>2</sub>H), 1 mL/min,  $\lambda$  = 254 nm, Rt (R)-**92** = 13.4 min & Rt (S)-**92** = 15.7 min). DABCO and Et<sub>3</sub>N failed to racemise (S)-**96** and (S)-**92**.

#### Scheme 97



The racemisation of the methyl ester (S)-**96** was also investigated using NaOH in 2-ethoxyethanol at 80 °C (**Scheme 98**). The level of hydrolysis of the methyl ester (S)-**96** to the acid (**92**) was incredibly high (61%) when 1 equivalent NaOH was used (**Table 20**). When the concentration of NaOH was decreased, the hydrolysed product was also decreased.

#### Scheme 98



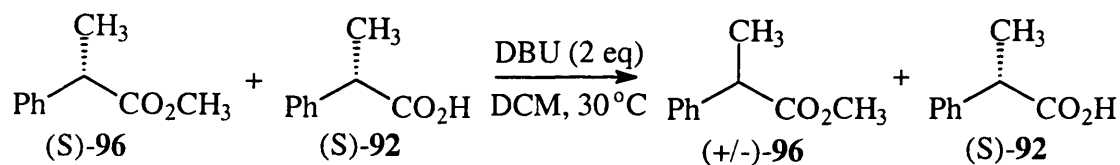
**Table 20.** Racemisation of the methyl ester (S)-**96** using NaOH in 2-ethoxyethanol

Entry	NaOH (eq)	Temp °C	Time (h)	% ee (S)- <b>96</b> <sup>a</sup>	% acid formed <sup>b</sup>
1	1.0	80	20	0	61
2	0.5	80	20	0	22
3	0.1	80	24	6	6
4	0.1	60	24	0	12

<sup>a</sup> Determined by chiral HPLC. <sup>b</sup> Determined by chiral HPLC and also resolved on the same column (ChiralCel OJ, 90:10 (Hex/IPA), 1 mL/min,  $\lambda$  = 254 nm,  $R_t$  = 11.8 min & 12.3 min).

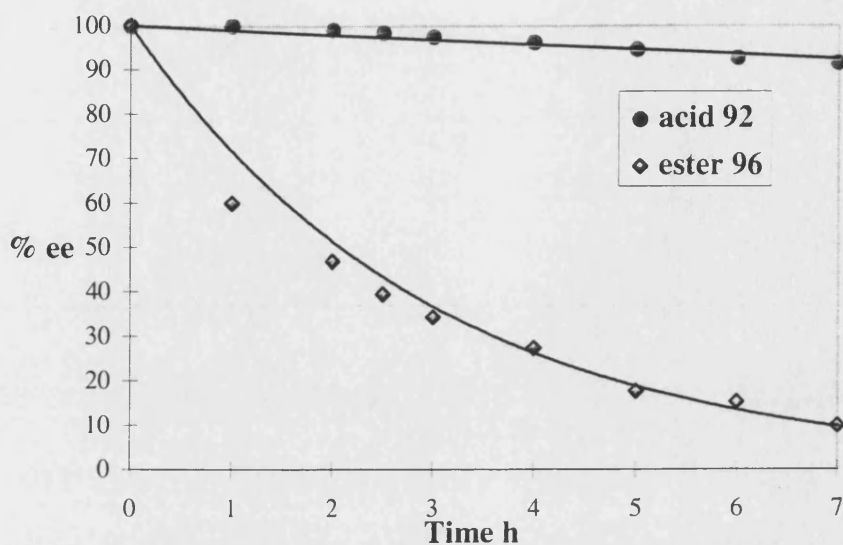
The racemisation of the methyl ester (S)-**96** in the presence of the acid (S)-**92** was conducted using DBU (2 eq) as the racemising agent (**Scheme 99**). After a 7 hour period (aliquots were removed during the reaction for chiral HPLC analysis), the ester (S)-**96** was completely racemised (10% ee remained), whereas the acid (S)-**92** was recovered in 92% ee (**Chart 2**).

**Scheme 99**





A plot of % ee Versus Time



**Chart 2.** Relative racemisation of (S)-**96** and (S)-**92** using DBU

Although we had successfully racemised the methyl ester (S)-**96** in preference of the acid (S)-**92**, the conditions employed were not gentle enough to be incorporated with an enzymatic hydrolysis reaction. Therefore the search for milder racemisation conditions continues...

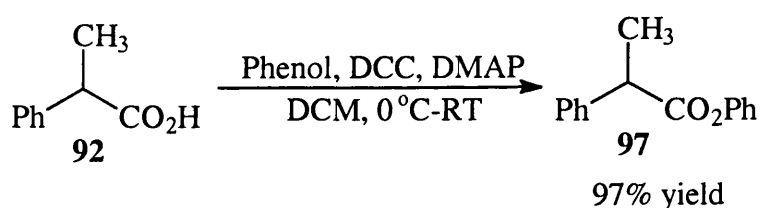
The attempted racemisation of the methyl ester (S)-**96** under basic buffered conditions (pH 8-11) failed to work. Even when the reactions were repeated with addition of Lewis acids ( $\text{MgCl}_2$ ,  $\text{CdCl}_2$ ,  $\text{CoCl}_2$  and  $\text{FeCl}_2$ ), no racemisation was observed (analysed by chiral HPLC).

### H.1.3 Racemisation of Phenyl Esters

We have postulated that having a phenyl ester moiety will enhance the acidity of the  $\alpha$ -proton, but the preparation of the phenyl ester (**97**) proved to be problematic.

Several attempts were tried to prepare the phenyl ester (**97**) (acid-catalysed, Mitsunobu reagents, acid chlorides) but the yields were disappointingly low with only 27-57%. Finally, the preparation of the phenyl ester (**97**) was achieved by coupling the acid (**92**) with phenol (1 eq) in the presence of DCC (1.1 eq) and a catalytic amount of DMAP. The phenyl ester (**97**) was obtained as colourless crystals (mp. 38-39 °C) in 97% yield (**Scheme 100**). No racemisation was observed when the acid (S)-**92** was coupled with phenol under the same reaction conditions to give (S)-**97**, also in near quantitative yield.

**Scheme 100**

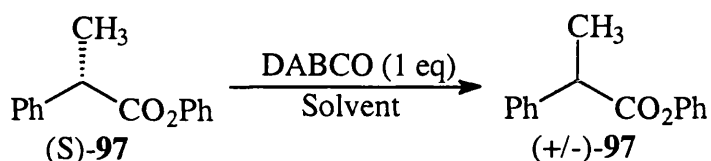


The phenyl ester (**97**) was identified by mass spectrometry MS (EI+)  $m/z = 226.2$  ( $M^+$ ), (found  $M^+$ , 226.0993  $\text{C}_{15}\text{H}_{14}\text{O}_2$  requires  $M^+$ , 226.0994), also determined by  $^1\text{H}$  and  $^{13}\text{C}$  NMR, IR and chiral HPLC ChiralPak AD column, 95:5 (Hex/IPA), 1 mL/min,  $\lambda = 254$  nm,  $R_t$  (S)-**97** = 5.9 min &  $R_t$  (R)-**97** = 6.3 min. According to  $^1\text{H}$  NMR data, the quartet of the  $\alpha$ -proton had shifted from 3.8 ppm (acid) to 4.0 ppm (product). This was a clear indication that the  $\alpha$ -proton of the phenyl ester (**97**) was more acidic than the acid (**92**).

The racemisation of the phenyl ester (S)-**97** proceeded adequately with DABCO (1 eq) in different solvents ranging from non-polar organic solvents to biphasic systems containing aqueous-organic mix (**Scheme 101**). Effective use of aqueous-organic

media, especially a water/MeCN mixture (1:19), had been successful for the DKR employing a lipase enzyme and DABCO.<sup>143</sup>

#### Scheme 101



**Table 21.** Racemisation of (S)-97 using DABCO (1 eq)

Entry	Solvent	Temp °C	Time (h)	% ee (S)-97 <sup>a</sup>
1	DMSO	40	24	2
2	cyclohexane	60	24	7
3	2-ethoxyethanol	60	24	15
4	DCM	60	24	89
5	water/DMSO (1:19)	40	45	6
6	buffer <sup>b</sup> /DMSO (1:19)	40	19	8
7	water/MeCN (1:19)	40	19	51
8	water/ <i>t</i> -BuOH (1:19)	40	19	89

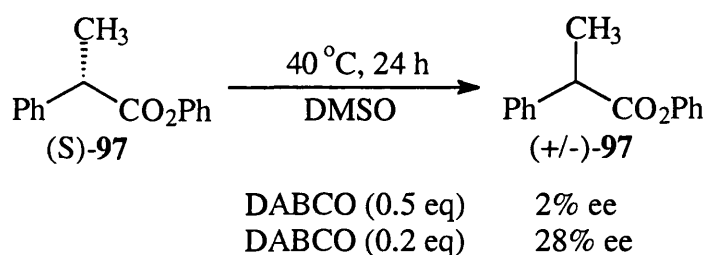
<sup>a</sup> Determined by chiral HPLC. <sup>b</sup> 10 mM sodium phosphate solution pH 7.0.

The data obtained (**Table 21**) illustrated that the rate of racemisation was dependent on the solvent system used. Most solvents tested gave near to complete racemisation after 24 hours (Entries 1-3), except DCM (Entry 4). The rate of racemisation in biphasic systems was best using water/DMSO or buffer/DMSO mixtures (Entries 5 & 6). Furthermore, the rate of racemisation was slower in water/MeCN and slower still in water/*t*-BuOH systems (Entries 7 & 8).

The effect of DABCO concentrations on the rate of racemisation was investigated. We have conducted the studies using (S)-97 with a sub-stoichiometric amount of DABCO in DMSO at 40 °C (**Scheme 102**). The reactions were stopped after 24

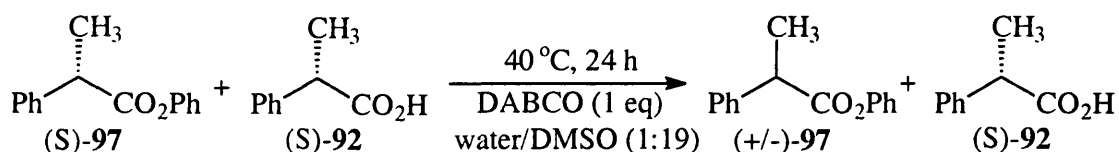
hours and analysed using chiral HPLC to determine the enantiomeric excess of the remaining ester (S)-**97**. It was revealed that even at low concentration of DABCO (0.2 eq), the enantiomeric purity of (S)-**97** had been reduced down to 28%. The racemisation of (S)-**97** was also performed in various aqueous-organic mixtures (1:1) using DABCO (0.1 eq) but the best result obtained was only 93% ee after 20 hours at 40 °C.

#### Scheme 102



The phenyl ester (S)-**97** was subjected to racemisation conditions where the acid (S)-**92** was also present. The reaction was run in water/DMSO (1:19) with DABCO (1 eq) at 40 °C (Scheme 103). During the progress of the reaction aliquots were taken to determine the enantiomeric purity of the ester (S)-**97** and the acid (S)-**92** using chiral HPLC.

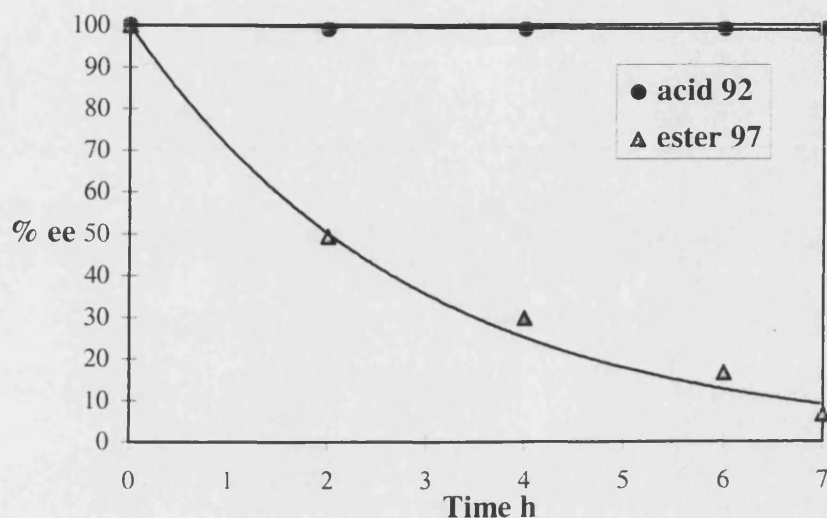
#### Scheme 103



Under reaction conditions containing DABCO, (S)-**92** did not racemise, but the phenyl ester (S)-**97** was rapidly racemised under 7 hours (Chart 3). Even when the

reaction was left for 28 hours, (S)-**92** was still recovered in >99% ee as indicated by chiral HPLC analysis.

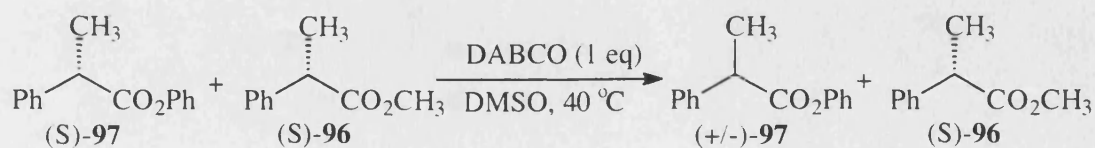
Plot of % ee Versus Time



**Chart 3.** Relative racemisation of (S)-**97** and (S)-**92** using DABCO

The rate of racemisation between the methyl ester (S)-**96** and the phenyl ester (S)-**97** was also compared using DABCO (1 eq) as the racemisation agent (**Scheme 104**). The experiment was conducted at 40 °C in DMSO and samples were removed during the reaction to determine the enantiomeric excess of the esters (analysed by chiral HPLC).

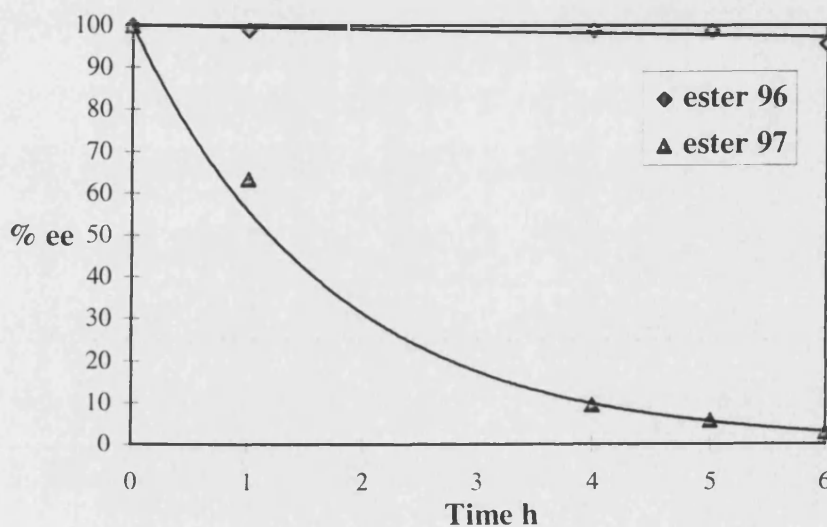
**Scheme 104**



The difference in the rates of racemisation between the methyl ester (S)-**96** and the phenyl ester (S)-**97** was noticeably high. The ester (S)-**96** was unaffected under basic

racemisation conditions containing DABCO and the enantiomeric excess of (S)-**96** was still 96% after 6 hours, compared with only 3% ee for (S)-**97**, as shown (**Chart 4**). Other bases such as BEMP supported on polystyrene also displayed good reaction rates for the racemisation of (S)-**97** and when triethylamine was used, the reaction proceeded very slowly.<sup>145</sup>

Plot of % ee Versus Time



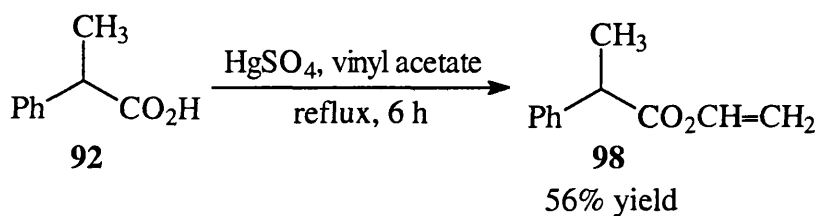
**Chart 4.** Relative racemisation of (S)-**97** and (S)-**96** using DABCO

#### D.1.4 Racemisation of Vinyl Esters

Vinyl esters have been known to undergo irreversible enzymatic transesterification reactions. The preparation of vinyl esters, however, has been disappointing because of poor yields and high impurities associated with these procedures. Since we require a single enantiomer of vinyl ester for the racemisation studies, the method used to prepare vinyl esters must be racemisation-free. The vinyl ester (**98**) was initially synthesised using a palladium-catalysed method. Although this procedure was mild and simple to conduct, the vinyl ester (**98**) was isolated in only 20% yield. The

preparation of the vinyl ester (**98**) using acid (**92**) catalysed by HgSO<sub>4</sub> in vinyl acetate (**Scheme 105**) was more successful and gave 56% isolated yield (yellow oil). No racemisation was observed when a single enantiomer of (S)-**98** was prepared.

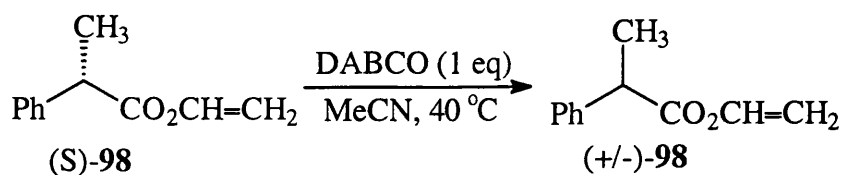
**Scheme 105**



The vinyl ester (**98**) was confirmed by mass spectrometry MS (EI+)  $m/z = 176.2(M^+)$  and analysis by <sup>1</sup>H NMR gave a doublet of doublets at 4.56 ppm, 4.85 ppm and 7.25 ppm, all with a single proton intensity indicating a CH=CH<sub>2</sub> moiety.

The vinyl ester (S)-**98** rapidly racemises under the influence of DABCO (1 eq) in MeCN at 40 °C (**Scheme 106**). During the reaction, samples were taken for HPLC analysis (using ChiralCel OJ, 90:10 (Hex/IPA), 1 mL/min,  $\lambda = 254$  nm, Rt (S)-**98** = 6.2 min & Rt (R)-**98** = 8.0 min) to determine the remaining enantiomeric purity of the vinyl ester (S)-**98**. The reaction was stopped after 24 hours and (S)-**98** was recovered in 13% ee.

## Scheme 106



Time (h)	% ee
0	91
3	57
4	44
6	43
24	13

The selective racemisation of the vinyl ester (S)-98 was conducted in the presence of (S)-96 using DABCO (1 eq) in MeCN. The enantiomeric excess, however, cannot be determined from HPLC analysis due to similar retention times between the vinyl ester (98) and the methyl ester (96) (both esters resolved under the same HPLC conditions).

Other substrates were also investigated and the *p*-nitrophenyl ester (S)-99 exhibits some racemisation (85% ee from 100% ee) under conditions containing trioctylamine (Oct<sub>3</sub>N) (1 eq) and toluene at room temperature for 24 hours. Trifluoroethyl ester (S)-100 did not racemise under conditions containing Oct<sub>3</sub>N but was racemised in the presence of DABCO (1 eq) in MeCN at room temperature to give 63% ee after 21 hours.

### D.1.5 Kinetic and Dynamic Kinetic Resolution of Esters

Successful resolutions of the methyl esters (96) have been reported using HLE,  $\alpha$ -chymotrypsin and CCL.<sup>117-118</sup> Since the ester (S)-96 only racemises under strongly basic conditions employing DBU, we have diverted our attention to focus on the



resolution of the phenyl ester (**97**) and esters that readily undergo racemisation under mild basic conditions.

## Phenyl Esters

Enzyme-catalysed hydrolyses of the ester (**97**) exhibit slow reaction rates and poor enantioselectivities. The laborious enzyme screening process was eventually narrowed down to CCL (or CRL) and CLEC-17 which gave good conversions and with high enantioselectivity for the hydrolysis of the ester (**97**). A general reaction scheme depicting an enzyme-catalysed hydrolysis of the phenyl ester (**97**) is shown below (Scheme 107).

Scheme 107

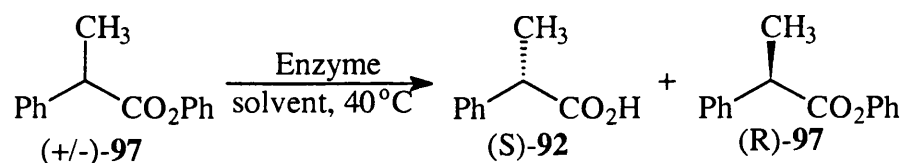


Table 22. Enzyme-catalysed hydrolysis of the phenyl ester (**97**)

Entry	Enzyme	Solvent	Time (h)	% Conv <sup>a</sup>	% ee ( <b>92</b> ) <sup>b</sup>	% ee ( <b>97</b> ) <sup>b</sup>
1	CCL	buffer/MeCN (2:1) <sup>c</sup>	192	48	94	90
2	CRL	H <sub>2</sub> O/MeCN (3:2)	528	55	92	82
3	CCL	buffer pH 8.8 <sup>d</sup>	22	60	38	100
4	CLEC-17	H <sub>2</sub> O/MeCN (1:7)	120	53	90	>99
5	CLEC-17	H <sub>2</sub> O/MeCN (10:1)	72	54	59	85
6	CLEC-20	H <sub>2</sub> O/MeCN (10:1)	72	95	5	-

<sup>a</sup> Determined by chiral HPLC based on the intensity of the phenol by-product.

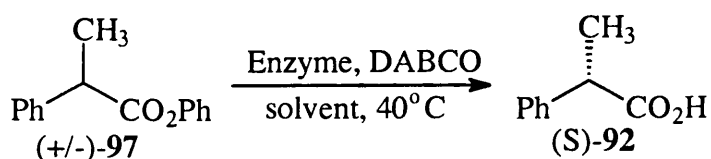
<sup>b</sup> Determined by Chiral HPLC. <sup>c</sup> 10 mM Phosphate buffer pH 8.0. <sup>d</sup> 10 mM Phosphate buffer solution at 30 °C.

The phenyl ester (**97**) was clearly a poor substrate for most enzymes because of its bulkiness. Only CCL has shown good conversions with moderate enantiomeric purity

ranging from 38% ee to 94% ee (**Table 22**, Entries 1-5). CLEC-20 (CLEC-PCL) displayed no enantiomeric discrimination, hence a 95% conversion in only 5% ee was obtained (Entry 6).

The DKR reactions have been tested against a variety of different biphasic solvent systems. DMSO was not used in the DKR reactions because of difficulty in removing the solvent after the reactions and due to the fact that enzymes react slowly in DMSO solutions.<sup>123</sup> The attempted DKR reactions were performed (**Scheme 108**) by vigorously stirring a combination of racemic (**97**), an enzyme and DABCO in aqueous-organic solvent mixture at 40 °C.

**Scheme 108**



**Table 23.** Attempted DKR of the phenyl ester (**97**)

Entry	Enzyme	Solvent	DABCO	Time (h)	% <sup>a</sup> Conv	% ee <sup>a</sup> (S)-92	% ee <sup>a</sup> (97)
1	CLEC-17	H <sub>2</sub> O/MeCN(1:3)	1.5 eq <sup>b</sup>	240	43	81	3
2	CCL	buffer/MeCN(2:1)	0.1 eq	336	37	>99	40
3	CLEC-17	H <sub>2</sub> O/MeCN(10:1)	Et <sub>3</sub> N <sup>c</sup>	165	73	31	78
4	CLEC-17	H <sub>2</sub> O/MeCN(10:1)	0.1 eq	165	88	20	83
5	CRL	Mix A	1 eq	144	89	19	-
6	α-CT	Mix A	1 eq	144	61	65	95

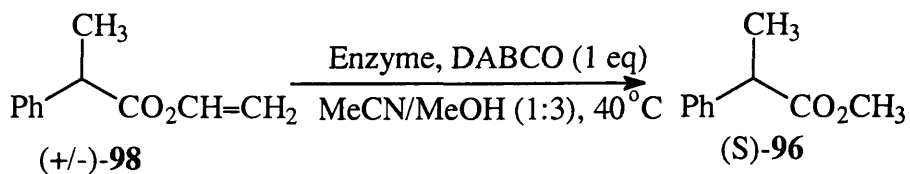
<sup>a</sup> Determined by chiral HPLC. <sup>b</sup> DABCO was added to the enzyme reaction after 48 h and more enzyme was added after 72 h and 168 h. <sup>c</sup> Et<sub>3</sub>N (1 eq) at RT. Mix A = 0.1 M phosphate buffer pH 7.0/cyclohexane/Et<sub>2</sub>O (8:1:1), (α-CT = α-chymotrypsin).

The acid (S)-**92** was obtained in 43% conversion with 81% ee (**Table 23**). Although the conversion was still below 50% and does not represent a working DKR, the starting material (**97**) was recovered as a racemic mixture (Entry 1). This has indicated that the racemisation of the phenyl ester (**97**) was happening during the enzymatic hydrolysis process. Although conversions >50% were obtained ranging from 73-89%, poor enantiomeric purities were observed (19-31%) (Entries 3-5). The attempted DKR reaction of racemic (**97**) using  $\alpha$ -chymotrypsin and DABCO (1 eq) gave 61% conversion in 65% ee of (S)-**92** (Entry 6). This was a good result obtained above 50% conversion, since a simple kinetic resolution reaction only gives a maximum of 80% ee. The results obtained are preliminary findings for the DKR of the phenyl ester (**97**). Further optimisation is necessary and the solvent systems used need to be studied in more detail in order to accomplish the overall goal.

### Vinyl Esters

Phenyl-(2-phenyl)butanoate (**101**) and *p*-nitrophenyl-(2-phenyl)butanoate (**102**) did not hydrolyse under enzymatic conditions. Furthermore, the attempted DKR of the vinyl ester (**98**) gave >95% conversion but with racemic product. Enzyme-catalysed transesterification of the vinyl ester (**98**) by methanol, coupled with the racemising agent (DABCO) (**Scheme 109**) proceeded well to give good conversion but with poor enantioselectivity (**Table 24**). The low enantiomeric purity of the product (S)-**96** could be explained due to the competing chemical transesterification reaction caused by DABCO. Further investigation, however, will be required to determine the actual cause for the low enantiomeric purity observed.

## Scheme 109



**Table 24.** Enzyme-catalysed transesterification of (**98**) in the presence of DABCO

Entry	Enzyme	% Conversion <sup>a</sup>	% ee ( <b>S</b> )- <b>96</b> <sup>b</sup>
1	PCL	>96	14
2	PCL	>95	1
3	Novozym SP435	67	24

<sup>a</sup> Determined by <sup>1</sup>H NMR. <sup>b</sup> Determined by chiral HPLC.

### D.1.6 Summary

It was shown that the acidity of the  $\alpha$ -proton can be enhanced by changing the ester moiety into one that possesses electron withdrawing ability. Selective racemisation of one ester in preference of another has been achieved. In the presence of the methyl ester (**S**)-**96**, the phenyl ester (**S**)-**97** was selectively racemised within several hours using DABCO. Similarly, the racemisation of the methyl ester (**S**)-**96** was achieved in the presence of the acid (**S**)-**92** under conditions containing DBU. The DKR of the phenyl ester (**97**) when conducted in the presence of DABCO and an enzyme gave 61-89% conversion with 19-65% ee.<sup>146</sup> The DKR results achieved are far from perfect and further investigations are necessary in order to produce an ideal DKR of  $\alpha$ -alkylaryl esters.

## **Chapter 5**

## I.1.0 Experimental

### I.1.1 General Experiment

Commonly used solvents were distilled before use. Ethyl acetate (EtOAc) and petroleum ether (boiling between 60 °C and 80°C) were distilled from calcium chloride. Dichloromethane (DCM) was distilled from phosphorus pentoxide. Most of the solvents used were stored in the presence of activated molecular sieves 4Å. Acetone, dimethyl sulfoxide (DMSO), dimethyl formamide (DMF), 2-ethoxyethanol, acetonitrile (MeCN), cyclohexane and tetrahydrofuran (THF) were all obtained from commercially available suppliers (mainly from Aldrich).

In general reagents and chemicals such as secondary alcohol substrates and transition metal catalysts were obtained from chemical suppliers. Lipase enzymes obtained from Fluka Aldrich were Lipase A, recombinant from *Candida antarctica* (EC3.1.1.3), lipase from *Candida lipolytica* (EC3.1.1.3), lipase from hog pancreas (PPL, EC3.1.1.3), lipase from *Pseudomonas cepacia* (EC3.1.1.3), lipase from *Pseudomonas fluorescens*, SAM-2 (EC3.1.1.3), esterase from hog liver, PLE (EC3.1.1.1) [pig liver esterase], esterase, immobilised on eupergit® C from hog liver, PLE on eupergit® C (EC3.1.1.1) [esterase, immobilised on oxiran acrylic beads from hog liver; pig liver esterase, immobilised on eupergit® C], esterase from horse liver, HLE (EC3.1.1.1), proteinase from *Bacillus subtilis* var. biotecnus A (EC3.4.21.14) [protease; *Subtilisin Carlsberg* from *Bacillus subtilis* var. biotecnus A; *Subtilo* peptidase A], α-chymotrypsin from bovine pancreas (EC3.4.21.1). *Candida cylindracea* lipase (CCL) or *Candida rugosa* lipase (CRL), protease from *Bacillus*

*licheniformis* and protease type XXIII from *Aspegillus oryzae* were bought from Sigma Aldrich. Cross-linked enzyme crystals (CLEC) were obtained from Altus Biologics.

Analytical thin layer chromatography (TLC) was carried out using aluminium backed plates coated with Merck Kieselgel 60 GF<sub>254</sub> neutral (Type E) silica. TLC plates were visualised under UV light or by staining with potassium permanganate solution, followed by heating. Flash column chromatography was performed using Merck Kieselgel 60 H silica or silicagel (0.035-0.07 mm) pore diameter ca. 6 nm obtained from Acros.

Infra-red spectroscopy was carried out using Nicolet FT-205 and Perkin Elmer 1600 Series FT-IR spectrometer in the range 4000-600 cm<sup>-1</sup>, with internal background scan. Spectra were recorded as thin film for oil samples or as a nujol mull for solids.  $\delta^1\text{H}$  NMR and  $\delta^{13}\text{C}$  NMR spectra were recorded using Bruker AC-250 (250 MHz), Bruker WH-400 (400 MHz), Jeol (270 MHz) and Jeol (400 MHz) instruments. High performance liquid chromatography (HPLC) was performed on SP thermoSeparation products spectraSERIES spectrometer and Spectra-Physics spectrometer; SP4290 Integrator, SP8700 Solvent Delivery System, and Spectra 100 Variable Wavelength Detector. Chiral columns used were ChiralCel OD, ChiralPak AD and ChiralCel OJ columns were obtained from Fisher Scientific supplier. Mass spectrometry analysis was carried out using a Micromass Autospec spectrometer.

### Preparation of (±)-1-acetoxy-1-phenylethane (**26**)

The racemic 1-phenylethan-1-ol (**25**) (10.00 g, 0.082 mol) in DCM (60 mL), triethylamine (2.5 mL, 0.09 mol) and a catalytic amount of DMAP (30 mg) were added to a 100 mL RB-flask fitted with a magnetic stirrer bar. To the reaction mixture acetic anhydride (9.3 mL, 0.09 mol) was added dropwise over a period of 5 minutes at room temperature. The reaction was stirred for 15 minutes. The extent of the reaction was monitored by TLC using 2:1 (petroleum ether/ether)  $R_f$  (**25**) = 0.42 and  $R_f$  (**26**) = 0.85 and stopped when no starting material could be detected. To the reaction mixture ice-water (50 mL) was added and left stirring for a further 5 minutes, then extracted with DCM (2 X 100 mL), washed with saturated ammonium chloride solution (2 X 50 mL), water (2 X 50 mL) and finally with brine (100 mL). The organic extracts were combined and dried over anhydrous magnesium sulfate, then concentrated under vacuum to afford a pale yellow oil of the acetate (**26**) (11.93 g, 0.073 mol, 89%). HPLC Chiralcel OD column, 99:1 (hexane/IPA),  $\lambda$  = 254 nm, 1 mL/min,  $R_t$  (R)-**26** = 5.10 min and  $R_t$  (S)-**26** = 5.50 min (Aldrich FT-NMR **1**(2), 1201C FT-IR **1**(3), 1335D).

### General procedure for enzymatic acylation reactions

To a 10 mL RB flask the racemic alcohol (**25**) (0.54 g, 4.39 mmol), vinyl acetate (1.5 mL) and crude PFL enzyme (15 mg) were added. The reaction mixture was then stirred for 21 hours at 40 °C. The enzyme was removed by a simple filtering process using DCM as eluent and removal of the excess solvent under reduced pressure gave a pale yellow oil containing both the reactant (**25**) and the acetate product (**26**). The acetate product (R)-**26** was obtained in 48% conversion with >99% ee (analysed by  $^1\text{H}$  NMR and chiral HPLC, respectively). The absolute configuration and the



enantiomeric purity of (**26**) was determined by co-injection of the known acetate (**S**)-**26** analysed by chiral HPLC ChiralCel OD column (99:1 hexane/IPA, 0.5 mL/min). The acetate product observed was mainly (**R**)-**27** ( $R_t$  = 5.10 min) and the alcohol recovered was (**S**)-**25** ( $R_t$  = 24.5 min observed on the same column under the same conditions).

### Reduction of acetophenone (**27**) using samarium <sup>t</sup>butoxide

#### *Preparation of samarium <sup>t</sup>butoxide (**50**)*

To a 0.2 M solution of di-*tert*-butyl peroxide (15  $\mu$ L, 0.08 mmol) in THF, 0.1 M SmI<sub>2</sub> solution in THF (1.6 mL, 0.16 mmol) was slowly added under a nitrogen atmosphere. The colour changed immediately from blue-green to light yellow and the reaction mixture was left stirring at room temperature for 10 min.

To the freshly prepared samarium catalyst mixture (**50**) (described above), the ketone (**27**) (0.20 g, 0.16 mmol) in IPA (4 mL) was slowly added using a cannula under a positive nitrogen pressure at room temperature. The temperature was then raised to 65 °C and the reaction contents were stirred for 5 hours. The reaction mixture was quenched with 0.2 M HCl solution (5 mL) and extracted with diethyl ether (2 X 50 mL). The organic extracts were combined and washed with water, brine and then 0.1 M sodium thiosulfate solution. The organic layers were collected and combined then dried over MgSO<sub>4</sub>. The excess solvent was evaporated under reduced pressure to give a yellow oil in 33% conversion, determined by <sup>1</sup>H NMR.

FT-IR  $\nu_{\max}/\text{cm}^{-1}$  (Thin layer), 3355 (m), 3029 (m), 2973 (m), 1451 (m), 1077 (s).  $\delta_{\text{H}}$  (250 MHz, CDCl<sub>3</sub>), 1.49 (3H, d, CH<sub>3</sub>,  $J$  = 6.6 Hz), 2.40 (1H, br, s, OH), 4.98 (1H, q, CH,  $J$  = 6.6 Hz), 7.21-7.37 (5H, m, Ar-H). HPLC was performed using ChiralCel OD column, 99:1 hexane/IPA,  $\lambda$  = 254 nm, 1mL/min,  $R_t$  (**R**)-**25** = 18.9 min and  $R_t$

(S)-**25** = 25.7 min. The ketone (**27**) also appeared at  $R_t$  = 7.0 min under the same HPLC conditions.

#### **Oxidation of the alcohol (**25**) using samarium <sup>t</sup>butoxide**

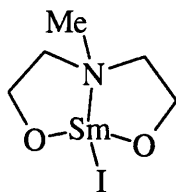
To the freshly prepared samarium <sup>t</sup>butoxide (**50**) solution (as described previously), the alcohol (**25**) (0.20 g, 0.16 mmol) and 2-butanone (8 mL) were added using a cannula under a positive nitrogen pressure. The reaction mixture was left under heated reflux for 68 hours and then quenched with 0.2 M HCl solution (5 mL) and extracted with diethyl ether (2 X 50 mL). The organic extracts were combined and washed with water, brine and 0.1 M sodium thiosulfate solution, then dried over MgSO<sub>4</sub>. Evaporation of the solvent under vacuum gave the ketone (**27**) in 19% conversion, analysed by <sup>1</sup>H NMR.

Analysis by TLC gave  $R_f$  (**27**) = 0.59 and  $R_f$  (**25**) = 0.39 using petroleum/diethyl ether (2:1) as eluent. FT-IR  $\nu_{\max}/\text{cm}^{-1}$  (Thin film) 3062(m), 1684(s), 1596(s), 1360(m), 1263(s).  $\delta_{\text{H}}$  (250 MHz, CDCl<sub>3</sub>), 2.60(3H, s, CH<sub>3</sub>), 7.43-7.96 (5H, m, Ar-H).

#### **Attempted racemisation of (R)-**25** using catalyst (**50**)**

To the catalyst (**50**) solution (prepared as described previously), (R)-**25** (0.060 g, 0.52 mmol) and the ketone (**27**) (0.060 g, 0.52 mmol) were added using a syringe. The reaction mixture was then stirred under a nitrogen atmosphere for 72 hours at room temperature. The crude product was collected after filtering through a pre-packed silica column using petroleum/diethyl ether (2:1) as eluent. After evaporation of all the solvent under reduced pressure, the alcohol (R)-**25** was recovered in 82% ee, determined by chiral HPLC.

### Preparation of modified Evan's catalyst (**52**)



To a RB-flask under nitrogen atmosphere containing 0.1 M samarium(II) iodide solution (1.0 mL, 0.1 mmol), di-iodoethane (0.015 mg, 0.053 mmol) was added and stirred at room temperature. The formation of samarium(III) iodide was indicated by a colour change from blue-green to yellow. To a second RB-flask containing *N*-methyl diethanolamine (**51**) in THF (0.5 mL, 0.1 mmol) at 0 °C was slowly added *n*-BuLi (18  $\mu$ L, 0.19 mmol). When the addition of *n*-BuLi was complete the temperature was raised to room temperature and the mixture was transferred using a cannula under a positive nitrogen pressure to the RB-flask containing the freshly prepared SmI<sub>3</sub>. THF (0.4 mL) was used to rinse the *O*-lithiated *N*-methyl diethanolamine solution and the reaction mixture was stirred for a further 1 hour.

The prepared catalyst (**52**) was used instantly by injecting the ketone (**27**) (0.10 g, 0.82 mmol) in IPA (5 mL) and stirred at 65 °C. After 24 hours, the catalyst was filtered and no reduction reaction was observed by <sup>1</sup>H NMR or by TLC.

### Reduction of the ketone (**27**) using aluminium isopropoxide

To a 25 mL RB-flask fitted with a condenser, the ketone (**27**) (0.12 g, 1.0 mmol) and aluminium isopropoxide (0.080 g, 10 mol%) were added in IPA (4 mL). The contents were stirred for 24 hours at 80 °C. The reaction mixture was quenched with 0.2 M HCl (10 mL) and extracted with ethyl acetate (2 X 50 mL), washed with water (50 mL) and then brine (50 mL). The organic layers were combined and dried over

anhydrous  $\text{MgSO}_4$ . Evaporation of the excess solvent yielded a pale yellow oil in 85% yield.

#### **Oxidation of the alcohol (25) using aluminium isopropoxide**

The alcohol (**25**) (0.50 g, 4 mmol), 2-butanone (0.72 mL, 8 mmol) and aluminium isopropoxide (0.080 g, 10 mol%) were all added to a 25 mL RB-flask containing cyclohexane (5 mL) fitted with a condenser. Using an oil bath the reaction mixture was heated to 83 °C and stirred for 24 hours. The reaction mixture was quenched with 0.2 M HCl solution (10 mL) and extracted with ethyl acetate (2 X 50 mL). The organic layers were collected and washed with water (50 mL), then brine (50 mL) and dried over anhydrous  $\text{MgSO}_4$ . Evaporation of the excess solvent under reduced pressure gave a pale yellow oil (63% conversion, determined by  $^1\text{H}$  NMR).

#### **A general procedure for the racemisation of (R)-25 using aluminium isopropoxide**

To a 25 mL RB-flask the alcohol (R)-**25** (0.12 g, 1.00 mmol), the ketone (**27**) (0.12 g, 0.99 mmol) and aluminium isopropoxide (0.040 g, 20 mol%) were added in cyclohexane (2 mL). The reaction mixture was heated to 82 °C with stirring and aliquots were removed during the course of the reaction and quenched with 0.2 M HCl solution (2 mL), then extracted with ethyl acetate (2 X 10 mL), washed with water (10 mL), and then brine (10 mL). The organic collections were combined and dried over anhydrous  $\text{MgSO}_4$ . After evaporation of the solvent, the recovered alcohol was analysed by chiral HPLC using ChiralCel OD column, 99:1 (Hex/IPA), 1 mL/min,  $R_t$  (R)-**25** = 21.0 min and  $R_t$  (S)-**25** = 28.1 min. After 72 hours only 5% ee of alcohol (R)-**25** was observed.

***In situ* racemisation using aluminium isopropoxide coupled with an enzymatic acylation reaction: A general procedure**

To a 25 mL RB-flask fitted with a condenser, the racemic alcohol (**25**) (0.12 g, 1.0 mmol), the ketone (**27**) (0.12 g, 0.99 mmol), aluminium isopropoxide (0.020 g, 10 mol%), lipase enzyme from *Pseudomonas fluorescens* (PFL) (15 mg), vinyl acetate (2 mL) and cyclohexane (1 mL) were added. The reaction mixture was stirred at 80 °C and aliquots were removed during the reaction to determine the enantiomeric excess of the alcohol (R)-**25** using chiral HPLC. The aluminium catalyst was removed by quenching with 0.2 M HCl solution (2 mL) and extracted with diethyl ether (2 X 10 mL). The organic collections were combined and washed with water (10 mL) and then brine (10 mL). After drying over anhydrous MgSO<sub>4</sub> the sample was filtered and the excess solvent was removed under reduced pressure. After 11 days the acetate (R)-**26** was obtained in 82% conversion with 13% ee and the remaining alcohol substrate (S)-**25** was recovered in 84% ee (determined by <sup>1</sup>H NMR and HPLC, respectively).

**Note:**

Enzymatic resolution was carried out at 80 °C using the racemic alcohol (**25**) (0.54 g, 4.39 mmol) and PFL (20 mg) in vinyl acetate/cyclohexane (2:1). The reaction was stirred for 24 hours. The enzyme was removed by simple filtration and evaporation of the excess solvent to give the acetate product (R)-**26** in 43% conversion and 95% ee.

**Aluminium-catalysed acylation reaction**

A combination of the racemic alcohol (**25**) (0.12 g, 1.0 mmol), aluminium isopropoxide (0.040 g, 20 mol%), vinyl acetate (2 mL) and cyclohexane (1 mL) was heated at 80 °C for 24 hours. The aluminium catalyst was then removed by filtering

over a pre-packed silica column using DCM as eluent. The filtrate was concentrated under a reduced pressure to give a pale yellow oil containing the acetate (**26**) in 86% conversion (determined by  $^1\text{H}$  NMR).

### **Preparation of diisopropoxyaluminium trifluoroacetate (DIPAT)**

Trifluoroacetic acid (5.60 g, 49.02 mmol) was added to a solution of aluminium isopropoxide (10.0 g, 49.02 mmol) in dry DCM (15 mL) in a 100 mL 3-neck RB-flask equipped with a pressure equalising funnel and fitted with a  $\text{CaCl}_2$  guard tube over a period of half an hour at room temperature. The reaction mixture was then stirred for a further 1 hour, during which the flask contents became viscous. The excess solvent was removed under vacuum to give DIPAT as a white powder (8.09 g, 64% yield). Decomposition analysis gave mp  $>220^\circ\text{C}$  (in agreement with the literature value).<sup>49</sup>

### **Racemisation of (S)-**25** using DIPAT**

To a solution of the alcohol (S)-**25** (0.036 g, 0.30 mmol) in cyclohexane (2 mL) in an ace-pressure tube was added DIPAT (0.077 g, 0.30 mmol). The reactants were stirred vigorously at  $82^\circ\text{C}$  for 48 hours. Then quenched with 0.2 M HCl solution (5 mL) and extracted with DCM (2 X 20 mL). The organic portions were combined and washed with water (30 mL), then brine (30 mL) and dried over anhydrous  $\text{MgSO}_4$ . Evaporation of excess solvent under vacuum obtained a yellow oil. The enantiomeric purity of the starting (S)-**25** was recovered in 56% ee and analysed by chiral HPLC using ChiralCel OD column, 99:1 (Hex/IPA), 1 mL/min,  $R_t(\text{R})\text{-}\mathbf{25} = 18.2$  min and  $R_t(\text{S})\text{-}\mathbf{25} = 24.5$  min.

### Dynamic kinetic resolution using DIPAT

To an ace-pressure tube, the racemic alcohol (**25**) (0.036 g, 0.30 mmol), PFL (15 mg) and vinyl acetate (2 mL) were added and stirred at 60 °C for 72 hours. Then DIPAT (0.077 g, 0.30 mmol) and the ketone (**27**) (0.036 g, 0.30 mmol) in cyclohexane (1 mL) were added and the reaction was allowed to stirred for another 48 hours. More PFL (10 mg) was added after 120 hours. Then the reaction was brought to a stop after 240 hours. The reaction mixture was acidified with 2.0 M HCl solution and extracted with DCM (2 X 50 mL), washed with water (50 mL) and then brine (50 mL). The solvent was evaporated under vacuum to give the crude acetate product in 77% conversion and 35% ee, determined by <sup>1</sup>H NMR and chiral HPLC, respectively.

### General procedure for the oxidation of (**26**) using rhodium catalyst.

Under nitrogen atmosphere [Rh(cod)Cl]<sub>2</sub> (4 mg, 2 mol%), *O*-phenanthroline ligand (0.013 g, 8 mol%) and KOH (9 mg, 20 mol%) in acetone (5 mL) were heated under reflux in a 25 mL RB-flask for 10 minutes under nitrogen. The colour of the reaction mixture changed from brown to blue. Then the alcohol (**25**) (0.10 g, 0.82 mmol) was added slowly using a syringe. The reaction mixture then turned a deep purple coloration. The reaction was left stirring and monitored by TLC using petroleum ether/diethyl ether (2:1) as eluent. The reaction was stopped after 1 hour by simply filtering off the catalyst through a pre-packed silica column using ethyl acetate as eluent. The ketone (**27**) was obtained in 63% conversion (determined by <sup>1</sup>H NMR).

### General procedure for the reduction of the ketone (**27**) using rhodium catalysts

Under a nitrogen atmosphere Rh<sub>2</sub>(OAc)<sub>4</sub>·2H<sub>2</sub>O (4 mg, 2 mol%) and *O*-phenanthroline ligand (13 mg, 8 mol%) in IPA (8 mL) were heated at reflux for 10

minutes. The colour of the reaction mixture changed from green to brown. The temperature was lowered to 60 °C and the ketone (**27**) (0.10 g, 0.83 mmol) and KOH (5 mg, 10 mol%) were added. The colour of the reaction mixture then changed to deep purple. The course of the reaction was monitored by TLC using petroleum ether/diethyl ether (2:1) as eluent. After 1 hour no starting material was observed. At the end of the reaction the catalyst was removed by filtering through a packed column of silica and flushed with ethyl acetate. <sup>1</sup>H NMR analysis gave >99% conversion.

#### **General racemisation procedure using rhodium complexes**

To a RB-flask Rh<sub>2</sub>(OAc)<sub>4</sub>·2H<sub>2</sub>O (4 mg, 3.0 mol%), *O*-phenanthroline ligand (0.012 g, 6 mol%) and KOH (0.011 g, 20 mol%) were added in DCM (1 mL). The catalyst was activated by stirring at 50 °C for 15 minutes under nitrogen, then (*S*)-**25** (0.13 g, 1.0 mmol) and the ketone (**27**) (0.12 g, 1.0 mmol) in DCM (1 mL) were added. The reaction was then stirred for 120 hours and the catalyst was removed at the by simple filtration through a plug of silica using DCM to elute the sample. Then the solvent was removed under reduced pressure and the enantiomeric purity was analysed using HPLC (the racemic alcohol was obtained).

#### **General procedure for enzyme and rhodium catalyst combination**

The racemic alcohol (**25**) (0.10 g, 0.82 mmol), the ketone (**27**) (0.10 g, 0.82 mmol), *O*-phenanthroline (16 mg, 10 mol%), activated Amberlite (0.10 g) and Rh(cod)Cl<sub>2</sub> (10 mg, 5 mol%) were stirred together under a nitrogen atmosphere in vinyl acetate (3.0 mL) and DCM (1.0 mL). Then PFL (10 mg) was added and the reaction was left stirring at 60 °C for 120 hours. Purification of the crude product was carried out by simple filtration through a pre-packed silica column using DCM as eluent. Removal



of the excess solvent under vacuum gave a yellow oil. The acetate product was obtained in 76% conversion and 80% ee (determined using  $^1\text{H}$  NMR and chiral HPLC, respectively).

#### **Activation of Amberlite IRA-904**

The amberlite IRA-904 chloride exchange resin (0.10g) was activated with saturated sodium hydroxide solution, washed with water (4 X 200 mL) and acetone (2 X 100 mL). The activated Amberlite was dried under reduced pressure for 3 hours and then stored in a desiccator for 2 days before use.

#### **General racemisation of alcohol (S)-25 using ruthenium catalysts**

To a 25 mL RB-flask containing  $\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$  (30 mg, 3 mol%), *O*-phenanthroline (10 mg, 5 mol%) and KOH (11 mg, 20 mol%) in DCM (1 mL) were added and stirred at 50 °C for 15 min under a nitrogen atmosphere. Then the alcohol (S)-**25** (0.13 g, 1.03 mmol) and the ketone (**27**) (0.13 g, 1.03 mmol) in DCM (5 mL) were slowly added to the reaction mixture using a syringe. At the end of the reaction the enzyme and the metal catalyst were removed by simple filtration through a plug of silica using DCM as eluent. Concentration of the filtrate recovered 71% yield of the starting material in 51% ee (analysed by chiral HPLC).

#### **A general procedure for the DKR using ruthenium catalysts**

To a small RB-flask, the racemic alcohol (**53**) (0.014 g, 1.0 mmol),  $\text{Ru}(\text{bipy})_2\text{Cl}_2$  (0.024 g, 5 mol%), KOH (0.017 g, 30 mol%) and CAL were added and stirred in vinyl acetate/DCM (2:1) at 32 °C under a nitrogen atmosphere. The extent of the reaction was monitored by taking small samples during the reaction. The catalyst was

removed by filtering over a plug of silica and DCM was used to elute the sample. The filtrate collected was concentrated under a reduced pressure to give an oil which was analysed using  $^1\text{H}$  NMR and chiral HPLC. The acetate (R)-**54** formed in 69% conversion with 73% ee after 6 days.

FT-IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (Thin Film), 3063(w), 2980(m), 1736(s), 1246(s).  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 270 MHz) 1.20(3H, d,  $\text{CH}_3$ ,  $J = 6.4$  Hz), 1.99(3H, s,  $\text{CH}_3$ ), 2.74(1H, dd,  $\text{CH}_2$ ,  $J = 6.4$  Hz &  $J = 6.4$  Hz), 2.93 (1H, dd,  $\text{CH}_2$ ,  $J = 6.4$  Hz &  $J = 6.4$  Hz), 5.14(1H, sextet,  $\text{CH}$ ,  $J = 6.4$  Hz), 7.19-7.35(5H, m, Ar-H).  $\delta_{\text{C}}$  NMR (67.8 MHz,  $\text{CDCl}_3$ ), 19.4( $\text{CH}_3$ ), 21.2( $\text{CH}_3$ ), 42.2( $\text{CH}_2$ ), 71.4( $\text{CH}$ ), 126.4(aromatic CH), 128.3(aromatic CH), 129.4(aromatic CH), 137.6(aromatic C), 170.5( $\text{C}=\text{O}$ ). HPLC using ChiralCel OD column, 99:1 (Hex/IPA), 1 mL/min,  $\lambda = 254$  nm,  $R_t = 5.0$  min and 6.7 min. The absolute configuration of (R)-**54** was determined by the disappearance of (R)-**53** ( $R_t = 14.9$  min), since the alcohol (S)-**53** (obtained commercially) has been analysed under the same HPLC conditions and gave  $R_t = 12.7$  min.

#### Attempted preparation of ruthenium catalyst (**40**)

$\text{Ru}_3(\text{CO})_{12}$  (0.64 g, 1.0 mmol), tetraphenylcyclopentadienone (1.54 g, 4.0 mmol) and toluene (10 mL) were placed in a 25 mL stainless steel reactor. Before the reactor was closed, the content was purged with nitrogen gas. Then the reaction mixture was heated at 160 °C for 24 hours, cooled to ambient temperature, and then purged with nitrogen gas to remove any dissolved carbon monoxide gas. The reactor was then closed and re-heated to the above temperature for another 24 hours. After cooling to room temperature, toluene was removed under vacuum and the residue was dissolved in DCM, then was passed through a column of silica. DCM was used to elute the

colourless intermediate [(tetraphenylcyclopentadienone)tricarbonylruthenium(0)] (0.10 g, 20% yield).

The colourless crystals obtained were stirred in acetone (10 mL) and saturated sodium carbonate solution (5 mL) for 2 hours at room temperature. The reaction mixture was neutralised with saturated ammonium chloride solution and the acetone was removed under vacuum. The residue was extracted with DCM (2 X 30 mL), separated and dried over anhydrous  $\text{MgSO}_4$  and then filtered. The excess solvent was removed under reduced pressure and column chromatography using DCM/petroleum ether (1:1) as eluent. The orange crystals collected (mp 147-149 °C) did not correspond to any of the literature data<sup>74a-b</sup> for the catalyst (**40**) ( $^1\text{H}$  NMR analysis showed no proton at -17.75 ppm which corresponds to Ru-H-Ru and IR spectrum did not display any CO peaks at 2035, 2010, 1980, 1970  $\text{cm}^{-1}$ ).

#### **General racemisation procedure using iridium catalysts**

Under a nitrogen atmosphere the alcohol (S)-**25** (0.12 g, 1.0 mmol) and the ketone (**27**) (0.12 g, 1.0 mmol) were added to a RB-flask containing  $[\text{Ir}(\text{coe})_2\text{Cl}]_2$  (13 mg, 3 mol%), *O*-phenanthroline ligand (10 mg, 5 mol%) and KOH (11 mg, 20 mol%) in DCM (1 mL). The reaction mixture was stirred at 50 °C for 24 hours. The iridium catalyst was removed at the end of the reaction by simple filtration over pre-packed silica column and flushed with DCM. After evaporation of solvent under reduced pressure, the alcohol was recovered in 70% yield with 8% ee (analysed using chiral HPLC).

### General procedure for iridium-catalysed racemisation combined with enzymatic resolution reaction

To a small RB-flask  $[\text{Ir}(\text{coe})_2\text{Cl}]_2$  (7 mg, 2 mol%), *O*-phenanthroline ligand (6 mg, 4 mol%), the racemic alcohol (**25**) (0.10 g, 0.81 mmol) and base activated Amberlite (0.10 g) were stirred at 60 °C for 30 min in cyclohexane (2 mL) under a nitrogen atmosphere. Then the ketone (**27**) (0.10 g, 0.81 mmol) and lipase from *Pseudomonas sp.* (8 mg) were added. The reaction was left to stir for a further 96 hours. The reaction mixture was purified by simple filtration through a short column of silica and flushed with DCM. The solvent was evaporated under reduced pressure to give a pale yellow oil. The acetate product (**R**)-**26** was obtained in 91% conversion with 3% ee (analysed by  $^1\text{H}$  NMR and Chiral HPLC, respectively). The recovered alcohol was obtained in 91% ee (also determined under the same HPLC conditions).

### Attempted DKR of (*E*)-4-phenyl-3-butene-2-ol (**55**)

To a 5 mL RB-flask the allylic alcohol (**55**) (0.15 g, 1 mmol), (*E*)-4-phenyl-3-butene-2-one (0.015 g, 0.10 mmol), *O*-phenanthroline (0.01 g, 0.05 mmol), KOH (0.011 g, 20 mol%),  $[\text{Ir}(\text{cod})\text{Cl}]_2$  (0.01 g, 3 mol%), immobilised lipase from *Candida antarctica* (20 mg), vinyl acetate (2 mL) and IPA/acetone (2:1) were stirred together under a nitrogen atmosphere at 50 °C. After 8 days the reaction mixture was purified by filtering over a pre-packed silica column to give the corresponding acetate product (**56**) at 76% conversion with 44% ee (analysed by  $^1\text{H}$  NMR and chiral HPLC).

FT-IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (Thin film), 3063(w), 2980(m), 1736(s), 1246(s).  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 270 MHz) 1.40(3H, d,  $\text{CH}_3$ ,  $J = 6.4$  Hz), 2.10(3H, s,  $\text{CH}_3$ ), 5.47(1H, p,  $\text{CH}$ ,  $J = 6.4$  Hz), 6.25(1H, dd,  $\text{CH}$ ,  $J = 6.4$  Hz, &  $J = 6.4$  Hz), 6.65 (1H, d,  $\text{CH}$ ,  $J = 16.2$  Hz), 7.20-

7.62(5H, m, Ar-H). HPLC ChiralCel OJ column, 99:1 (Hex/IPA), 1 mL/min,  $\lambda$  = 254 nm,  $R_t$  = 15.8 min and 20.4 min.

### 1-Phenethyl butanoate (58)

The alcohol (**25**) (0.50 g, 4.1 mmol), triethylamine (0.63 mL, 4.3 mmol) and a catalytic amount of DMAP (10 mg) in DCM (5 mL) were stirred together at room temperature. To the reaction mixture butyric anhydride (0.72 mL, 4.3 mmol) was added dropwise over a period of 5 minutes. After 3 hours the reaction mixture was quenched with ice-water, extracted with DCM (2 X 20 mL) and washed with 10 % sodium hydroxide solution (30 mL), water (30 mL) and then brine (30 mL). The combined organic layers were collected and dried over  $MgSO_4$ , filtered, and concentrated under reduced pressure. The butyrate product (**58**) was obtained as a pale yellow oil (0.73 g, 92% yield).

FT-IR  $\nu_{max}/cm^{-1}$  (Thin film), 3033(w), 2970(m), 1736(s), 1182(s).  $\delta_H$  ( $CDCl_3$ , 270 MHz) 0.90(3H, t,  $CH_3$ ,  $J$  = 7.2 Hz), 1.45(3H, d,  $CH_3$ ,  $J$  = 6.6 Hz), 1.50-1.70(2H, m,  $CH_2$ ), 2.25(2H, t,  $CH_2$ ,  $J$  = 4.6 Hz), 5.92(1H, q,  $CH$ ,  $J$  = 6.6 Hz), 7.25-7.35(5H, m, Ar-H).  $\delta_C$  NMR (67.8 MHz,  $CDCl_3$ ), 13.6( $CH_3$ ), 18.4( $CH_2$ ), 22.2( $CH_3$ ), 35.4( $CH_2$ ), 76.5(CH), 126.0(aromatic CH), 127.7(aromatic CH), 128.4(aromatic CH), 141.8(aromatic C), 172.9(C=O). Chiral HPLC ChiralCel OD column, 100% Hexane, 1 mL/min,  $\lambda$  = 254 nm,  $R_t$  = 7.5 min and 8.1 min.

### Iridium-catalysed acylation reaction

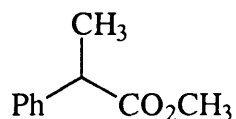
The alcohol (**25**) (0.1 g, 0.83 mmol),  $[Ir(coe)_2Cl]_2$  (74 mg, 10 mol%) *O*-phenanthroline (33 mg, 20 mol%), KOH (5 mg, 10 mol%) were stirred in vinyl acetate (5 mL) under a nitrogen atmosphere at 50 °C for 4 days. The catalyst was

removed by filtering over a plug of silica using DCM for elution. The solvent was removed under reduced pressure to give a yellow oil (**26**) in 76% conversion (determined by  $^1\text{H}$  NMR).

### General procedure for the racemisation of secondary alcohols using a universal ketone

To a small RB-flask the alcohol (S)-**25** (0.12 g, 1.0 mmol),  $[\text{Ir}(\text{cod})\text{Cl}]_2$  (13 mg, 3 mol%), *O*-phenanthroline (8 mg, 4 mol%), KOH (9 mg, 20 mol%) in cyclohexane/DCM (1:1) were added and stirred under reflux under a nitrogen atmosphere for 1.5 hours. Then benzophenone (**59**) (0.09 g, 0.5 mmol) in DCM was slowly added using a syringe. After a further 3.5 hours, the iridium catalyst was removed by simple filtration through a column of silica using DCM to elute the sample. After evaporation of the excess solvent under reduced pressure the recovered alcohol (R)-**25** was obtained in 1% ee (determined by chiral HPLC).

### Methyl-(2-phenyl)propionate (**96**)



To a 100 mL RB-flask the acid (**92**) (0.50 g, 3.33 mmol), methanol (20 mL) and *p*-toluenesulfonic acid (50 mg, 0.26 mmol) were added and stirred under reflux. The reaction was monitored by TLC using 3:1 (petroleum ether/ethyl acetate) as eluent ( $R_f$  product = 0.77). The reaction went to completion after 5 hours and quenched with saturated sodium bicarbonate solution, extracted with DCM (2 X 50 mL), washed with water and then brine. The organic layer was and dried over  $\text{MgSO}_4$  and

concentrated under reduced pressure. The product methyl-(2-Phenyl)propionate (**96**) was obtained as a pale yellow oil (0.53 g, 3.23 mmol, 97%).

FT-IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (Thin film) 3028(m), 2982(m), 1737(s), 1167(s).  $\delta_{\text{H}}$  (270 MHz,  $\text{CDCl}_3$ ) 1.50(3H, d,  $\text{CH}_3$ ,  $J = 7.1$  Hz), 3.66(3H, s,  $\text{CH}_3$ ), 3.71(1H, q,  $\text{CH}$ ,  $J = 7.1$  Hz), 7.20-7.45(5H, m, Ar-H).  $\delta_{\text{C}}$  (67.8 MHz,  $\text{CDCl}_3$ ) 18.5( $\text{CH}_3$ ), 45.4( $\text{CH}_3$ ), 51.9( $\text{CH}$ ), 127.1(aromatic CH), 127.4(aromatic CH), 128.6(aromatic CH), 140.5(aromatic C), 175.0( $\text{C}=\text{O}$ ).<sup>118</sup> HPLC using ChiralCel OJ column, 90:10 (Hex/IPA), 1 mL/min, Rt (R)-**96** = 7.5 min and Rt (S)-**96** = 8.6 min.

#### **Racemisation of the methyl ester (S)-96**

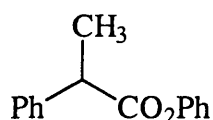
In an ace-pressure tube (S)-**96** (14 mg, 0.09 mmol), and NaOH (0.4 mg, 0.9 mmol) in 2-ethoxyethanol (0.5 mL) were stirred at 80 °C for 24 hours. The reaction mixture was quenched with 0.2 M HCl solution, then extracted with DCM (2 X 20 mL). The organic collections were combined and washed with water, then brine and dried over anhydrous  $\text{MgSO}_4$ . The solvent was evaporated under vacuum to give the recovered methyl ester in 6% ee. HPLC analysis were performed on ChiralCel OJ column, 90:10 (Hex/IPA), 1 mL/min, Rt = 8.6 min for (R)-**96** and 9.7 min for (S)-**96**.

#### **Racemisation of the methyl ester (S)-96 in the presence of the acid (S)-92**

(S)-**96** (50 mg, 0.3 mmol) and (S)-**92** (50 mg, 0.3 mmol) were stirred in DCM (2 mL) at 30 °C in the presence of DBU (92 mg, 0.6 mmol). Aliquots were removed during the reaction and quenched with 1.0 M HCl aqueous solution, extracted with DCM and washed with water and then brine. The organic layers were combined and dried over anhydrous  $\text{MgSO}_4$ . The solvent was removed under reduced pressure and analysed using chiral HPLC (see chart 2). HPLC ChiralCel OD column, 97.98:2:0.02

(Hex/IPA/HCO<sub>2</sub>H), 1 mL/min,  $\lambda$  = 254 nm, Rt (R)-**92** = 13.4 min and Rt (S)-**92** = 15.7 min. HPLC ChiralCel OJ column, 90:10 (Hex/IPA), 1 mL/min,  $\lambda$  = 254 nm, Rt (R)-**96** = 7.5 min and Rt (S)-**96** = 8.6 min.

### Preparation of phenyl-(2-phenyl)propionate (**97**) by acid catalysis



The acid (**92**) (0.15 g, 1.0 mmol), phenol (0.40 g, 4.25 mmol) and *p*-toluenesulfonic acid (30 mg) were heated under reflux in cyclohexane (5 mL) for 20 hours. The reaction mixture was quenched with saturated sodium bicarbonate solution (30 mL) and extracted with DCM (2 X 30 mL), washed with water and then brine. The organic layers were collected and dried over MgSO<sub>4</sub>, then concentrated under reduced pressure. Purification of the crude product was performed by column chromatography using 3:1 (petroleum ether/diethyl ether) as the eluent. The product was collected in the first fraction (*R*<sub>f</sub> = 0.68). The phenyl ester (**97**) was obtained in 33% yield (0.076 g, 0.34 mmol).

M.p. 38-39 °C. (MS (EI<sup>+</sup>) *m/z* = 226.2(M<sup>+</sup>). (Found M<sup>+</sup>, 226.0993 C<sub>15</sub>H<sub>14</sub>O<sub>2</sub> requires M<sup>+</sup>, 226.0994). FT-IR  $\nu_{\text{max}}$ /cm<sup>-1</sup> (Thin film) 3061(m), 1756(s), 1594(m), 1141 (s).  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 400 MHz), 1.63(3H, d, CH<sub>3</sub>, *J* = 7.0 Hz), 4.00(1H, q, CH, *J* = 7.0 Hz), 7.20-7.45(10H, m, Ar-H).  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 100 MHz), 18.5(CH<sub>3</sub>), 45.4(CH), 121.5(aromatic CH), 125.9(aromatic CH), 127.7(aromatic CH), 128.7(aromatic CH), 129.3(aromatic CH), 140.1(aromatic C), 152.0(C-O), 173.4(C=O). HPLC Chiralpak AD column, 95:5 (Hex/IPA), 1 mL/min,  $\lambda$  = 254 nm, Rt (S)-**97** = 5.9 min and Rt (R)-**97** = 6.3 min.



### **Preparation of (97) using the Mitsunobu method**

In a 3-neck RB-flask diethylazodicarboxylate (DEAD) (0.17g, 1.0 mmol) and triphenylphosphine (0.26 g, 1.0 mmol) in THF (4 mL) were stirred under nitrogen atmosphere at room temperature for 1 hour. To the reacting mixture, acid (**92**) (0.15 g, 1.0 mmol) in THF (3 mL) was added slowly through an addition funnel and the orange solution turned bright pink. The reaction was stirred for a further 1 hour, then phenol (94 mg, 1.0 mmol) in THF (3 mL) was added. The extent of the reaction was monitored by TLC. The crude product mixture was quenched with saturated sodium bicarbonate solution (20 mL) and extracted with DCM (2 X 30 mL), washed with water and then brine. The organic layers were combined, dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The ester (**97**) was obtained in 32% yield (0.072 g, 0.32 mmol).

### **Preparation of (97) using oxalyl chloride**

The acid (**92**) (0.15 g, 1.0 mmol), phenol (94 mg, 1.0 mmol), triethylamine (0.14 mL, 1.0 mmol) in dry DCM (1 mL) were stirred at 0 °C under a nitrogen atmosphere for 15 minutes. To the reaction mixture oxalyl chloride (0.1 mL, 1.0 mmol) was added very slowly using a 1 mL syringe. The colourless solution turned yellow after the addition of oxalyl chloride. Then a drop of dimethyl formamide (DMF) was added and the reaction was stirred at 0 °C for a further 5 minutes. The temperature was raised to 40 °C and the reaction mixture was left stirring for 20 hours. The solvent was evaporated under high vacuum at the end of the reaction. The product (**97**) was obtained after purification using column chromatography (0.13 g, 0.57 mmol, 57% yield).

### **Preparation of (97) using DCC coupling method**

The acid (92) (0.50 g, 3.33 mmol) in anhydrous DCM (2 mL), a catalytic amount of DMAP (30 mg) and phenol (0.31 g, 3.33 mmol) were added to a pre-dried ace-pressure tube. The solution was stirred at 0 °C while DCC (0.69 g, 3.33 mmol) was added slowly. The reaction was kept at 0 °C for 10 minutes then 20 hours at room temperature. The urea precipitate was filtered over a pre-packed silica column using cold ether as eluent. This procedure was repeated when more precipitate was formed. The residue was evaporated under vacuum to give (97) as a light yellow oil (0.58 g, 3.23 mmol, 97% yield).

### **Racemisation of phenyl ester (S)-97**

To a small RB-flask (S)-97 (23 mg, 0.1 mmol) and DABCO (6 mg, 0.05 mmol) were added in DMSO (1 mL) and stirred at 40 °C for 24 hours. The reaction was acidified with 0.2 M HCl solution and extracted with DCM (2 X 20 mL). The organic collections were combined and washed with water, then brine and dried over anhydrous MgSO<sub>4</sub>. The solvent was evaporated under vacuum and the extent of racemisation was analysed using chiral HPLC. The recovered ester (S)-97 was obtained in 2% ee.

### **Selective racemisation of phenyl ester (S)-97 in the presence of acid (S)-92**

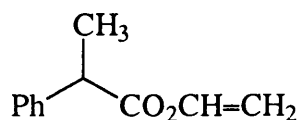
The phenyl ester (S)-97 (0.14 g, 0.60 mmol) and the acid (S)-92 (0.090 g, 0.60 mmol) were stirred in water/DMSO (1:19) in the presence of DABCO (0.071 g, 0.06 mmol) at 30 °C. During the course of the reaction, samples were removed, acidified using 0.1M HCl solution and extracted with diethyl ether. The organic layers were combined,

dried over anhydrous  $\text{MgSO}_4$  and evaporated under reduced pressure and then analysed using chiral HPLC. The results obtained are shown in chart 3.

#### **Selective racemisation of the phenyl ester (S)-97 in the presence of the methyl ester (S)-96**

The phenyl ester (S)-97 (0.080 g, 0.33 mmol) and the methyl ester (S)-96 (0.060 g, 0.33 mmol) were stirred in DMSO (2 mL) in the presence of DABCO (0.040 g, 0.33 mmol) at 40 °C. During the course of the reaction, samples were removed, neutralised using 0.1 M HCl solution and extracted with DCM. The organic layers were combined, dried over anhydrous  $\text{MgSO}_4$  and evaporated under a reduced pressure and then analysed using chiral HPLC. The results obtained are shown in chart 4.

#### **Mercuric salt catalysed formation of vinyl-(2-phenyl)propionate (98)**



A mixture of the acid (92) (1.00 g, 6.67 mmol), mercury acetate (0.85 g, 2.67 mmol) and concentrated  $\text{H}_2\text{SO}_4$  (11  $\mu\text{L}$ , 22 mmol) in vinyl acetate (15 mL) was refluxed for 6 hours under nitrogen atmosphere. At the end of the reaction, saturated sodium acetate solution (100 mL) was used to quench the reaction and then extracted with ether (3 X 50 mL), washed with water and finally with brine. The solvent was removed under vacuum and the residue was purified through a pre-packed silica gel column using petroleum ether/ether (6:1) as eluent. The product (98) was obtained as an oil (0.66 g, 0.38 mmol, 56% yield).<sup>112</sup>

MS (EI+)  $m/z = 176.2(M^+)$ . (Found  $M^+$ , 176.0841,  $C_{11}H_{11}O_2$  requires 176.0793). FT-IR  $\nu_{\max}/\text{cm}^{-1}$  (Thin film) 3033(m), 2983(m), 1750(s), 1646(s), 1156(s).  $\delta_H$  NMR (270 MHz,  $\text{CDCl}_3$ ), 1.55(3H, d,  $\text{CH}_3$ ,  $J = 7.3$  Hz), 3.8(1H, q,  $\text{CH}$ ,  $J = 7.3$  Hz), 4.56(1H, dd,  $\text{CH}$ ,  $J = 1.6$  &  $J = 6.4$  Hz), 4.85(1H, dd,  $\text{CH}$ ,  $J = 1.6$  &  $J = 13.9$  Hz), 7.25(1H, dd,  $\text{CH}$ ,  $J = 6.2$  &  $J = 8.4$  Hz), 7.20-7.45(5H, m, Ar-H).  $\delta_C$  NMR (67.8 MHz,  $\text{CDCl}_3$ ), 18.4( $\text{CH}_3$ ), 45.2( $\text{CH}$ ), 97.0( $\text{CH}_2$ ), 127.3(aromatic CH), 127.5(aromatic CH), 128.7(aromatic CH), 139.7(aromatic C), 141.3( $\text{CH}$ ), 171.6( $\text{C=O}$ ). HPLC chiralCel OJ column, 90:10 (Hex/IPA), 1 mL/min,  $R_t$  (S)-**98** = 6.2 min and  $R_t$  (R)-**98** = 8.0 min.

#### **Preparation of the vinyl ester (98) using Palladium catalyst**

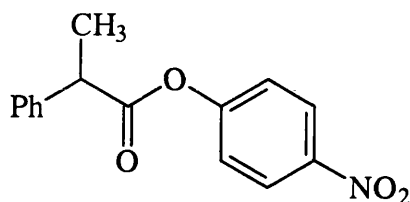
A mixture of the acid (**92**) (1.50 g, 10 mmol), vinyl acetate (100 mL, 1.08 mol), palladium acetate (0.35 g, 1.56 mmol) and KOH (56 mg, 1 mmol) were stirred in a 250 mL RB-flask at room temperature for 24 hours. The reaction mixture was filtered through a pre-packed silica column and the residue was washed with vinyl acetate (20 mL). After evaporation of the excess vinyl acetate under vacuum, the crude product was purified by flash chromatography using silica gel and petroleum ether/ethyl acetate (3:1) was used as the eluent. The yellow oil collected in the first fraction was the vinyl ester (**98**) in 20% yield (0.35 g, 1.97 mmol).

#### **Racemisation of the vinyl ester (S)-98**

The vinyl ester (S)-**98** (0.02 g, 0.1 mmol) and DABCO (0.010 g, 0.1 mmol) were stirred together in MeCN (1 mL) at 40 °C. Aliquots were removed during the reaction and neutralised using 0.1 M HCl solution, and then extracted with DCM. The organic layers were combined, dried over anhydrous  $\text{MgSO}_4$  and evaporated

under a reduced pressure. (S)-**98** was recovered in 13% ee after 24 hours, analysed using chiral HPLC (see scheme 106).

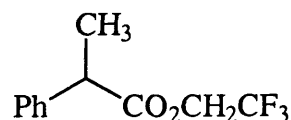
***p*-Nitrophenyl-(2-phenyl)propionate (**99**)**



The acid (**92**) (1.50 g, 0.01 mol) in anhydrous DCM (30 mL), MeCN (1.5 mL), a catalytic amount of DMAP (30 mg) and *p*-nitrophenol (1.40 g, 0.01 mol) were added to a pre-dried ace-pressure tube. The solution was stirred at 0 °C while DCC (2.10 g, 0.01 mol) was added slowly. During the addition of DCC, a cream precipitate was formed and the reaction was kept at 0 °C for 10 minutes then 24 hours at room temperature. The urea precipitate was filtered over a pre-packed silica column using cold ether as eluent. This procedure was repeated when more precipitate was formed. The residue was evaporated under vacuum to give a cream powder (2.75 g, 0.10 mol, 96% yield). Recrystallisation in hexane/IPA gave colourless needles of (**99**) in 60% yield.

M.p. 54-55 °C. (MS (CI+)  $m/z$  = 272.2(M<sup>+</sup>). (Found M<sup>+</sup>, 271.0847 C<sub>15</sub>H<sub>13</sub>NO<sub>4</sub> requires M<sup>+</sup>, 271.0845). FT-IR  $\nu_{\text{max}}/\text{cm}^{-1}$  (Thin film) 3038(m), 2968(m), 1760(s), 1525(s), 1130(s).  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 270 MHz) 1.62(3H, d, CH<sub>3</sub>, J = 8.0 Hz), 3.99(1H, q, CH, J = 8.0 Hz), 7.17 (2H, d, Ar-H, J = 9.2 Hz), 7.3-7.4(5H, m, Ar-H), 8.22(2H, d, Ar-H, J = 9.2 Hz).  $\delta_{\text{C}}$  (CDCl<sub>3</sub>, 67.8 MHz) 18.3(CH<sub>3</sub>), 45.6(CH), 122.2(aromatic CH), 125.1(aromatic CH), 127.4(aromatic CH), 127.7(aromatic CH), 128.9(aromatic CH), 138.3(aromatic C), 145.2(aromatic C-N), 155.5(aromatic C-O), 172.1(C=O).

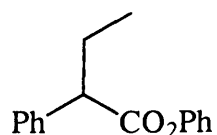
### Trifluoroethyl-(2-phenyl)propionate (100)



To a 100 mL RB-flask the acid (**92**) (0.10 g, 6.66 mmol), 2,2,2-trifluoroethanol (20 mL) and *p*-toluenesulfonic acid (50 mg, 0.26 mmol) were added and stirred under reflux. The reaction was stopped after 6 hours and quenched with saturated sodium bicarbonate solution, extracted with DCM (2 X 50 mL), washed with water and then brine. The organic collections were combined and dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The product trifluoroethyl ester (**100**) was obtained as a yellow oil (1.30 g, 5.96 mmol, 89%).

(MS (EI+)  $m/z$  = 232.2(M+). (Found  $M^+$ , 232.0707 C<sub>11</sub>H<sub>11</sub>O<sub>2</sub>F<sub>3</sub> requires  $M^+$ , 232.0711). FT-IR  $\nu_{\max}/\text{cm}^{-1}$  (Thin film) 3065(m), 2940(m), 1756(s), 1283(s), 1158(s), 973(s).  $\delta_{\text{H}}$  (270 MHz, CDCl<sub>3</sub>) 1.57(3H, d, CH<sub>3</sub>,  $J$  = 5.5 Hz), 3.81(1H, q, CH,  $J$  = 5.5 Hz), 4.30-4.60(2H, m, CH<sub>2</sub>), 7.20-7.40(5H, m, Ar-H).  $\delta_{\text{C}}$  (67.8 MHz, CDCl<sub>3</sub>) 18.3(CH<sub>3</sub>), 45.0(CH), 53.4(CH<sub>2</sub>), 120.8(CF<sub>3</sub>), 127.4(aromatic CH), 128(aromatic CH), 139.3(aromatic C), 172.9(C=O).

### Phenyl-(2-phenyl)butanoate (101)

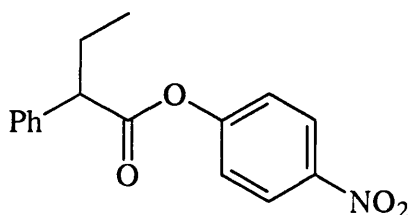


2-Phenylbutanoic acid (5.0 g, 0.03 mol) in anhydrous DCM (50 mL), a catalytic amount of DMAP (30 mg) and phenol (2.85 g, 0.03 mol) were added to a pre-dried ace-pressure tube. The solution was stirred at 0 °C while DCC (6.19 g, 0.03 mol) was added slowly and a white precipitated was observed. The reaction was kept at 0 °C

for 10 minutes then 21 hours at room temperature. The urea precipitate was filtered over a pre-packed silica column using cold ether as eluent. The residue was evaporated under vacuum to give **(101)** as a colourless oil (7.29 g, 0.03 mol, >99% yield).

(MS (EI+)  $m/z$  = 240.1. (Found  $M^+$ , 240.1160  $C_{16}H_{16}O_2$  requires 240.1150). FT-IR  $\nu_{max}/cm^{-1}$  (Thin film) 3083(m), 2968(m), 1754(s), 1139(s).  $\delta_H$  ( $CDCl_3$ , 270 MHz) 1.00(3H, t,  $CH_3$ ,  $J$  = 7.3 Hz), 1.92(1H, app. heptet,  $CH_2$ ,  $J$  = 7.5 Hz), 2.20(1H, app. heptet,  $CH_2$ ,  $J$  = 7.5 Hz), 3.68(1H, app. t,  $CH$ ,  $J$  = 7.3 Hz), 6.98-7.35(10H, m, Ar-H).  $\delta_C$  ( $CDCl_3$ , 67.8 MHz) 12.1( $CH_3$ ), 26.7( $CH_2$ ), 53.5( $CH$ ), 121.4(aromatic CH), 125.7(aromatic CH), 127.4(aromatic CH), 127.9(aromatic CH), 128.7(aromatic CH), 129.3(aromatic CH), 138.6(aromatic C), 150.7(aromatic C-O), 172.5(C=O).

#### ***p*-Nitrophenyl-(2-phenyl)butanoate (102)**



2-Phenylbutanoic acid (5.0 g, 0.03 mol) in anhydrous DCM (50 mL), MeCN (20 mL), a catalytic amount of DMAP (30 mg) and *p*-nitrophenol (4.17 g, 0.03 mol) were added to a pre-dried ace-pressure tube. The solution was stirred at 0 °C while DCC (6.19 g, 0.03 mol) was added slowly. A cream precipitate was formed and the reaction was kept at 0 °C for 10 minutes then 20 hours at room temperature. The urea precipitate was filtered over a pre-packed silica column using cold ether as the eluent. This procedure was repeated when more precipitate was formed. The residue was

evaporated under vacuum to give a yellow oil of (**102**) (8.70 g, 0.03 mol, >99% yield).

(MS (EI+)  $m/z$  = 285.1(M+). (Found  $M^+$ , 285.1001  $C_{16}H_{14}NO_4$  requires 285.1001).

FT-IR  $\nu_{\max}/\text{cm}^{-1}$  (Thin film) 3083(m), 2968(m), 1761(s), 1525(s), 1130(s).  $\delta_H$  ( $CDCl_3$ , 270 MHz) 1.00(3H, t,  $\underline{CH_3}$ ,  $J$  = 7.3 Hz), 1.95(1H, app. heptet,  $\underline{CH_2}$ ,  $J$  = 7.5 Hz), 2.25(1H, app. heptet,  $\underline{CH_2}$ ,  $J$  = 7.5 Hz), 3.72(1H, app. t,  $\underline{CH}$ ,  $J$  = 7.3 Hz), 7.19(2H, d, Ar- $\underline{H}$ ,  $J$  = 9.1 Hz), 7.30-7.50(5H, m, Ar- $\underline{H}$ ), 8.25(2H, d, Ar- $\underline{H}$ ,  $J$  = 9.1 Hz).  $\delta_C$  ( $CDCl_3$ , 67.8 MHz) 12.0( $CH_3$ ), 26.5( $CH_2$ ), 53.4( $CH$ ), 122.3(aromatic CH), 125.1(aromatic CH), 127.7(aromatic CH), 127.9(aromatic CH), 128.9(aromatic CH), 132.6(aromatic C), 137.8(aromatic C-N), 145.2(aromatic C-O), 171.6(C=O).

#### General procedure for the enzymatic hydrolysis of the phenyl ester (**97**)

A mixture of the racemic phenyl ester (**97**) (0.11 g, 0.5 mmol) and CCL (200 mg) was stirred together in 0.1 M phosphate buffer pH 8.0 (5 mL) and MeCN (2.5 mL) mix at 40 °C for 192 hours. The reaction mixture was adjusted to pH 2.0 using 2.0 M HCl solution, then extracted with DCM (2 X 20 mL), washed with water, brine and then dried over anhydrous  $MgSO_4$ . The solvent was removed under a reduced pressure to give the crude product. The acid (S)-**92** was determined with 48% conversion in 94% ee (analysed by chiral HPLC using ChiralCel OD column, 97.98:2:0.02 (Hex/IPA/ $HCO_2H$ ), 1 mL/min,  $\lambda$  = 254 nm,  $R_t$  (R)-**92** = 13.4 min and  $R_t$  (S)-**92** = 15.7 min, conversion was based on the formation of the by-product phenol  $R_t$  = 27.5 min (also resolved under the same HPLC conditions).



### General procedure for the DKR of esters

The racemic phenyl ester (**97**) (23 mg, 0.1 mmol) in MeCN (1 mL) and CLEC-17 (10 mg) were added to a 10 mL RB-flask with water (1 mL). The reaction was stirred vigorously for 48 hours at 40 °C. After this time DABCO (17 mg, 0.15 mmol) in MeCN (2 mL) with more CLEC-17 (10 mg) were added and the reaction mixture was left stirring for another 120 hours. More CLEC-17 (20 mg) was added after a total of 168 hours. After 240 hours, the reaction was stopped by adjusting the reaction mixture to pH 2.0 using 1.0 M HCl aqueous solution and extracted with DCM (2 X 20 mL), washed with water and then brine. The organic layers were combined and dried over MgSO<sub>4</sub>. The solvent was evaporated under reduced pressure to give the crude product in 43% conversion and 81% ee to the acid (S)-**92** (the recovered ester (**97**) was still racemic, determined using chiral HPLC).

### Transesterification reactions coupled with *in situ* racemisation

To an ace-pressure tube the racemic vinyl ester (**98**) (35 mg, 0.2 mmol) and Novozym SP 435 (100 mg) were added and stirred in dry MeOH (3 mL) and MeCN (1 mL) at 40 °C in the presence of DABCO (22 mg, 0.2 mmol). The reaction was stopped after 7 days. The reaction mixture was neutralised with 0.1 M HCl solution, washed with water and the organic layers were combined and dried over MgSO<sub>4</sub>. The crude product was obtained after removal of the solvent under vacuum. The methyl ester (S)-**96** was determined with 67% conversion in 24% ee, see table 24 (analysed by <sup>1</sup>H NMR and chiral HPLC, respectively).

## References

- 1) *Enzymatic reaction mechanisms* ed. Walsh, C. W. H. Freeman and company, San Francisco, **1979**.
- 2) Goergens, U. and Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1991**, 1064-1066.
- 3) Master, H. E.; Newadkar, R. V.; Rane, R. A. and Kumar, A. *Tetrahedron Lett.* **1996**, *37*, 9253-9254.
- 4) Goergen, U. and Schneider, M. P. *Tetrahedron: Asymmetry* **1992**, *3*, 525-528.
- 5) Robertson, D. W.; Krushininski, J. H.; Fuller, R. W. and Leander, J. D. *J. Med. Chem.* **1988**, *31*, 1412 and references cited therein.
- 6) Lundell, K. and Kanerva, L. T. *Tetrahedron: Asymmetry* **1995**, *6*, 2281-2286.
- 7) Wünsche, K.; Schwaneberg, U.; Bornscheuer, U. T. and Meyer, H. H. *Tetrahedron: Asymmetry* **1996**, *7*, 2017-2022.
- 8) Hsu, S.-H.; Wu, S.-S.; Wong, C.-H. and Wang, Y.-W. *Tetrahedron Letters* **1990**, *31*, 6403-6406 and cited therein.
- 9) Chênevert, R. and Courschesne, G. *Tetrahedron: Asymmetry* **1995**, *6*, 2093-2096.
- 10) a) Sharma, A.; Pawar, A. S. and Chattopadhyay, S. *Synth. commun.* **1996**, *26*, 19-25; b) Kang, S.-K.; Jeon, J.-H.; Yamaguchi, T.; Kim, J.-S. and Ko, B.-S. *Tetrahedron: Asymmetry* **1995**, *6*, 2139-2142.
- 11) Chadha, A.; Goergens, U. and Schneider, M. P. *Tetrahedron: Asymmetry* **1993**, *4*, 1449-1450.
- 12) Carpenter, B. E.; Hunt, I. R. and Keay, B. A. *Tetrahedron: Asymmetry* **1996**, *7*, 3107-3108.

- 13) Bovara, R.; Carrea, G.; Ferrara, L. and Riva, S. *Tetrahedron: Asymmetry* **1991**, *2*, 931-938.
- 14) *Enzyme Catalysis in Organic Synthesis. A Comprehensive Handbook* ed. Drauz, K. and Waldmann, H. VCH, Weinheim, **1995**, Vol. 1, 165-343.
- 15) a) Chen, C. S.; Fujimoto, Y.; Girdaukas, G. and Sih, C. *J. Am. Chem. Soc.* **1982**, *104*, 7294-7299; b) Martin, V. S.; Woodward, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M. and Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237-6240.
- 16) Hsu, S-H.; Wu, S-S.; Wong, C-H. and Wang, Y-W. *Tetrahedron Lett.* **1990**, *31*, 6403-6406.
- 17) Bevinakatti, H. S.; Banerji, A. A. and Newadkar, R. V. *J. Org. Chem.* **1989**, *54*, 2453-2455.
- 18) Lundh, M.; Nordin, O.; Hedenstrom, E. and Hogberg, H-E. *Tetrahedron: Asymmetry* **1995**, *6*, 2237-2244.
- 19) Ema, T.; Maeno, S.; Takaya, Y.; Sakai, T and Utaka, M. *Tetrahedron: Asymmetry* **1996**, *7*, 625-628.
- 20) Faraldos, J.; Arroyo, E. and Herradon, B. *Synlett* **1997**, 367-370.
- 21) Kita, Y.; Maeda, H.; Omori, K.; Okuno, T. and Tamura, Y. L. *Chem. Soc. Perkin Trans. 1* **1993**, 2999-3005.
- 22) Kita, Y.; Takebe, Y.; Murata, K.; Naka, T. and Akai, S. *Tetrahedron Lett.* **1996**, *37*, 7369-7372.
- 23) Faber, K. and Riva, S. *Synthesis* **1992**, 895-910.
- 24) Schudok, M. and Kretzschmar, G. *Tetrahedron Lett.* **1997**, *38*, 387-388.
- 25) Hoff, B. H.; Anthonsen, H. W. and Anthonsen, T. *Tetrahedron: Asymmetry* **1996**, *7*, 3187-3192.

- 26) Miyazawa, T.; Kurita, S.; Ueji, S.; Yamada, T. and Kuwata, S. *J. Chem. Soc. Perkin Trans. 1* **1992**, 2253-2255.
- 27) Naemura, K.; Fukuda, R.; Murata, M.; Konishi, M.; Hirose, K. and Tobe, Y. *Tetrahedron: Asymmetry* **1995**, 6, 2385-2394 and cited therein.
- 28) Gupta, A. K. and Kazlauskas, R. J. *Tetrahedron: Asymmetry* **1993**, 4, 879-888.
- 29) Burgess, K. and Jennings, L. D. *J. Am. Chem. Soc.* **1991**, 113, 6129-6139.
- 30) Naemura, K.; Murata, M.; Tanaka, R.; Yano, M.; Hirose, K. and Tobe, Y. *Tetrahedron: Asymmetry* **1996**, 7, 3285-3294.
- 31) Hultin, P. G. and Jones, J. B. *Tetrahedron Lett.* **1992**, 33, 1399-1402.
- 32) a) Egri, G.; Baitz-Gacs, E. and Poppe, L. *Tetrahedron: Asymmetry* **1996**, 7, 1437-1448; b) Ebert, C.; Ferluga, G.; Gardossi, L.; Gianferrara, T. and Linda, P. *Tetrahedron: Asymmetry* **1992**, 3, 903-912.
- 33) Lemke, K.; Theil, F.; Kunath, A. and Schick, H. *Tetrahedron: Asymmetry* **1996**, 7, 971-974.
- 34) Bis, S. J.; Whitaker, D. T. and Johnson, R. C. *Tetrahedron: Asymmetry* **1993**, 4, 875-878.
- 35) Kellogg, R. M. in *Comprehensive Organic Synthesis* ed. Trost, B. M.; Fleming, I. Pergamon, Oxford **1991**, Vol. 7, 305-325 and Vol. 8, 551-558.
- 36) *Lanthanides in Organic Synthesis* ed. Imamoto, T. Academic Press, **1994**.
- 37) Wilds, A. L. *Org. React.* **1944**, 2, 178-223.
- 38) Young, R. and Doering, W. V. E. *J. Am. Chem. Soc.* **1950**, 72, 637.
- 39) Djerassi, C. *Org. React (N.Y)* **1951**, 6, 207-235.
- 40) a) Iyer, S. and Varghese, J. P. *J. Chem. Soc., Chem. Commun.* **1995**, 465-466; b) Upadhyay, T. T.; Katdare, S. P.; Sabde, D. P.; Ramaswanmy, V. and Sudalai, A. *Chem. Commun.* **1997**, 1119-1120; c) Nishide, K.; Shigeta, Y.; Obata, K.; Inoue, T.

- and Node, M. *Tetrahedron Lett.* **1996**, 37, 2271-2274 and cited therein; d) Eliel, E. L. and Schroeter, S. H. *J. Am. Chem. Soc.* **1965**, 87, 5031-5038.
- 41) a) Zheng, B. and Srebnik, M. *J. Org. Chem.* **1995**, 60, 3278-3279; b) Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M.; Hunziker, D. and Petter, W. *Helv. Chim. Acta* **1992**, 75, 2171-2208.
- 42) Li, G.; Li, T. and Xu, Y. *Chem. Commun.* **1996**, 497-498.
- 43) a) Lebrun, A.; Namy, J-L. and Kagan, H. *Tetrahedron Lett.* **1991**, 32, 2355-2358; b) Namy, J- L.; Souppe, J.; Collin, J. and Kagan, H. B. *J. Org. Chem. Soc.* **1984**, 49, 2045-2049.
- 44) Girard, P. and Kagan, H. B. *J. Am. Chem. Soc.* **1980**, 102, 2693-2698.
- 45) a) Zhang, F-Y.; Yip, C-W. and Chan, A. S. C. *Tetrahedron: Asymmetry* **1996**, 7, 2463-2466; b) Okawa, H.; Katsuki, T.; Nakamura, M.; Kumagai, N.; Shuin, Y.; Shinmyoz, T. and Kida, S. *J. Chem. Soc., Chem. Commun.* **1989**, 139-140; c) Evans, D. A. and Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, 112, 6447-6449.
- 46) Evans, D. A.; Nelson, S. G.; Gagne, M. R. and Muci, A. R. *J. Am. Chem. Soc.* **1993**, 115, 9800-9801.
- 47) Watt, I.; Whittleton, S. N. and Whitworth, S. M. *Tetrahedron* **1986**, 42, 1047-1062.
- 48) Fujita, M.; Takarada, Y.; Sugimura, T. and Tai, A. *J. Chem. Soc., Chem. Commun.*, **1997**, 1631-1632.
- 49) Akamachi, G. K.; Varalakshmy, N. R. and Chaudhari, B. A. *Synlett* **1997**, 371-372.
- 50) Akamanchi, K. G. and Chaudhari, B. A. *Tetrahedron Lett.* **1997**, 38, 6925-6928.
- 51) Zassinovich, G. and Mestroni, G. *Chem. Rev.* **1992**, 92, 1051-1069.

- 52) Kvintovics, P.; James, B. R. and Heil, B. *J. Chem. Soc., Chem. Commun.* **1986**, 1810-1811.
- 53) Gladiali, S.; Pinna, L.; Delogu, G.; Martin, S. D.; Zassinovich, G. and Mestroni, G. *Tetrahedron: Asymmetry* **1990**, *1*, 638-648.
- 54) a) Newman, L. M. and Williams, J. M. J.; McCague, R. and Potter, G. A. *Tetrahedron: Asymmetry* **1996**, *7*, 1597-1598; b) Langer, T.; Janssen, J. and Helmchen, G. *Tetrahedron: Asymmetry* **1996**, *7*, 1599-1602.
- 55) Nishiyama, H.; Yamaguchi, S.; Kondo, M. and Itoh, K. *J. Org. Chem. Soc.* **1992**, *57*, 4306-4309.
- 56) a) Spogliarich, R.; Kaspar, J. and Graziani, M. *J. Organomet. Chem.* **1986**, *306*, 407-412; b) Spogliarich, R.; Kaspar, J. and Graziani, M. *J. Catalysis* **1985**, *94*, 292-296.
- 57) a) Gamez, P.; Fache, F. and Lemaire, M. *Tetrahedron: Asymmetry* **1995**, *6*, 705-718; b) Gamez, P.; Fache, F.; Mangeney, P. and Lemaire, M. *Tetrahedron Lett.* **1993**, *34*, 6897-6898; c) Gamez, P.; Dunjic, B. and Lemaire, M. *J. Org. Chem. Soc.* **1996**, *61*, 5196-5197.
- 58) a) Zassinovich, G. and Grisoni, F. *J. Organomet. Chem.* **1983**, *247*, C24-C26; b) Zassinovich, G.; Camus, A. and Mestroni, G. *J. Organomet. Chem.* **1977**, *133*, 377-384.
- 59) Bottecchi, C. *J. Organomet. Chem.* **1986**, *304*, 217-225.
- 60) a) Gladiali, S.; Chelucci, G. and Soccolini, F. *J. Organomet. Chem.* **1989**, *370*, 285-294; b) Gladiali, S.; Chelucci, G.; Chessa, G.; Delogu, G. and Soccolini, F. *J. Organomet. Chem.* **1987**, *327*, C15-C17.

- 61) a) Uson, R.; Oro, L. A.; Sario, R. and Esteruelas, M. A. *J. Organomet. Chem.* **1981**, *214*, 399-404; b) Spogliarich, R.; Zassinovich, G.; Mestroni, G. and Graziani, M. *J. Organomet. Chem.* **1979**, *179*, C45-C47.
- 62) Almeida, M. L. S.; Kocovsky, P. and Bäckvall, J-E. *J. Org. Chem.* **1996**, *61*, 6587-6590.
- 63) a) Gautier, I.; Ratovelomanana-Vidal, V.; Savignac, P. and Genet, J-P. *Tetrahedron Lett.* **1996**, *37*, 7721-7724; b) Tranchier, J-P.; Ratovelomanana-Vidal, V.; Genet, J-P.; Tong, S. and Cohen, T. *Tetrahedron Lett.* **1997**, *38*, 2951-2954.
- 64) Ohkuma, T.; Ooka, H.; Ikariya, T. and Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417-10418.
- 65) Wang, G-Z. and Bäckvall, J-E. *J. Chem. Soc., Chem. Commun.* **1992**, 980-982 and cited therein.
- 66) Wang, G-Z. and Bäckvall, J-E. *J. Chem. Soc., Chem. Commun.* **1992**, 337-339.
- 67) Karlsson, U.; Wang, G-Z. and Bäckvall, J-E. *J. Org. Chem.* **1994**, *59*, 1196-1198.
- 68) a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T. and Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521-2522; b) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T. and Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562-7563; c) Haack, K-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T. and Noyori, R. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 285-288.
- 69) Puntener, K.; Schwink, L. and Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 8165-8168.
- 70) Langer, T. and Helmchen, G. *Tetrahedron Lett.* **1996**, *37*, 1381-1384.
- 71) Hashiguchi, S.; Fujii, A.; Haack, K-J.; Matsumura, K.; Ikariya, T. and Noyori, R. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 288-290.

- 72) a) Chowdhury, R. L. and Bäckvall, J-E. *J. Chem. Soc., Chem. Commun.* **1991**, 1063-1064; b) Bäckvall, J-E.; Chowdhury, R. L. and Karlsson, U. *J. Chem. Soc., Chem. Commun.* **1991**, 473-475.
- 73) Sasson, Y. and Blum, J. *J. Org. Chem.* **1975**, *40*, 1887-1896.
- 74) a) Menashe, N. and Shvo, Y. *Organometallics* **1991**, *10*, 3885-3891; b) Shvo, Y.; Czarkie, D. and Rahamim, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7400-7402.
- 75) a) Almeida, M. L. S.; Beller, M.; Wang, G-Z. and Bäckvall, J-E. *Chem. Eur. J.* **1996**, *2*, 1533-1536; b) Wang, G-Z.; Andreasson, U. and Bäckvall, J-E. *J. Chem. Soc., Chem. Commun.* **1994**, 1037-1038.
- 76) Larsson, A. L. E.; Persson, B. A. and Bäckvall, J-E. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1211-1212.
- 77) Muller, D.; Umbricht, G.; Weber, B. and Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 132-241.
- 78) Schnider, P.; Koch, G.; Pretot, R.; Wang, G.; Bohnen, F. M.; Kruger, C. and Pfaltz, A. *Chem. Eur. J.* **1997**, *3*, 887-892.
- 79) Zassinovich, G. and Mestroni, G. *J. Mol. Catal.* **1987**, *42*, 81-90.
- 80) Brunner, H. *Synthesis* **1988**, 645-654.
- 81) Krause, H. W. and Bhatnagar, A. K. *J. Organomet. Chem.* **1986**, *302*, 265-267.
- 82) a) Martin, S. D.; Zassinovich, G. and Mestroni, G. *Inorg. Chim. Acta* **1990**, *174*, 9-11; b) Zassinovich, G.; Bianco, C. D. and Mestroni, G. *J. Organomet. Chem.* **1981**, *222*, 323-329; c) Mestroni, G.; Zassinovich, G.; Camus, A. and Martinelli, F. *J. Organomet. Chem.* **1980**, *198*, 87-96; d) Martinelli, F.; Mestroni, G.; Camus, A. and Zassinovich, G. *J. Organomet. Chem.* **1981**, *220*, 383-392.



- 83) a) Bellemin-Laponnaz, S.; Grisie, H.; Ny, J. P. L. and Osborn, J. A. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 976-978; b) Lorber, C. Y. and Osborn, J. A. *Tetrahedron Lett.* **1996**, *37*, 853-856.
- 84) Chabardes, P.; Kuntz, E. and Varagnat, J. *Tetrahedron* **1977**, *33*, 1775-1783.
- 85) a) Garner, C. M.; Mendez, N. Q.; Kowalczyk, J. J.; Fernandez, J. M.; Emerson, K.; Larsen, R. D. and Gladysz, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 5146-5160; b) Dewey, M. A.; Bakke, J. M. and Gladysz, J. A. *Organometallics* **1990**, *9*, 1349-1351; c) Buhro, W. E.; Georgiou, S.; Fernandez, J. M.; Patton, A. T.; Strouse, C. E. and Gladysz, J. A. *Organometallics* **1986**, *5*, 956-965; d) Agbossou, S. K.; Smith, W. W. and Gladysz, J. A. *Chem. Ber.* **1990**, *123*, 1293-1299; e) Patton, A. T.; Strouse, C. E.; Knobler, C. B. and Gladysz, J. A. *J. Am. Chem. Soc.* **1983**, *105*, 5804-5811.
- 86) Koh, J. H.; Jeong, H. M. and Park, J. *Tetrahedron Lett.* **1998**, *39*, 5545-5548.
- 87) Deen, H. V. D.; Cuiper, A. D.; Hof, R. P.; Oeveren, A. V.; Feringa, B. L. and Kellogg, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 3801-3803.
- 88) Heuvel, M. V. D.; Cuiper, A. D.; Deen, H. V. D.; Kellogg, R. M. and Feringa, B. L. *Tetrahedron Lett.* **1997**, *38*, 1655-1658.
- 89) Davis, A. P. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 591-594.
- 90) Stecher, H. and Faber, K. *Synthesis* **1997**, 1-17.
- 91) Caddick, S. and Jenkins, K. *Chem. Soc. Rev.* **1996**, 447-456.
- 92) Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475-1490.
- 93) Inagaki, M.; Kiratake, J.; Nishioka, K. and Oda, J. *J. Org. Chem.* **1992**, *57*, 5643-5649.
- 94) Reetz, M. and Schimossek, K. *Chimia* **1996**, *50*, 668-669.
- 95) Allen, J. V. and Williams, J. M. J. *Tetrahedron Lett.* **1996**, *37*, 1859-1862.

- 96) Dinh, P. M.; Howarth, J. A.; Hudnott, A. R. and Williams, J. M. J. *Tetrahedron Lett.* **1996**, *37*, 7623-7626.
- 97) Stürmer, R. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1173-1174.
- 98) Fuji, K. and Kawabata, T. *Chem. Eur. J.* **1998**, *4*, 373-376.
- 99) Ahmed, A.; Bragg, R. A.; Clayden, J.; Lai, L. W.; McCarthy, A.; Pink, J. H.; Westlund, N. and Yasin, S. A. *Tetrahedron* **1998**, *54*, 13277-13294.
- 100) Shaw, J. E.; Kunerth, D. and Sherry, J. J. *Tetrahedron Lett.* **1973**, 689-692.
- 101) Holmberg, K. and Hansen, B. *Tetrahedron Lett.* **1975**, 2303-2306.
- 102) Ono, N.; Yamada, T.; Saito, T.; Tanaka, K. and Kaji, A. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2401-2404.
- 103) Neises, B. and Steglich, W. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 522-524.
- 104) Balcom, B. J. and Petersen, N. O. *J. Org. Chem.* **1989**, *54*, 1922-1927.
- 105) Milkolajczyk, M. and Kielbasinski, P. *Tetrahedron* **1981**, *37*.
- 106) a) Davis, A. P.; Dresen, S. and Lawless, L. J. *Tetrahedron Lett.* **1997**, *38*, 4305-4308; b) Kurihara, T.; Nakajima, Y. and Mitsunobu, O. *Tetrahedron Lett.* **1976**, 2455-2458.
- 107) Kise, H. and Shirato, H. *Tetrahedron Lett.* **1985**, *26*, 6081-6084.
- 108) Haslam, E. *Tetrahedron* **1980**, *36*, 2409-2433.
- 109) Neelakantan, S.; Padmasani, R. and Seshadri, T. R. *Tetrahedron* **1965**, *21*, 3531-3536.
- 110) Adams, J. H.; Lewis, J. R. and Paul, J. G. *Synthesis* **1979**, 429-430.
- 111) Alderman, R. L. *J. Org. Chem.* **1949**, *14*, 1057-1073 and cited therein.
- 112) a) Bairgrie, L. M.; Leung-Toung, R. and Tidwell, T. T. *Tetrahedron Lett.* **1988**, *29*, 1673-1676; b) Gong, L.; Leung-Toung, R. and Tidwell, T. T. *J. Org. Chem.* **1990**, *55*, 3634-3639.

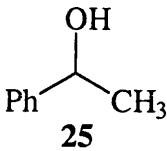
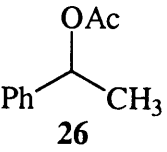
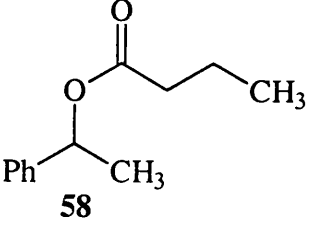
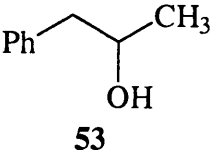
- 113) Weinhouse, M. and Janda, K. D. *Synthesis* **1993**, 81-83.
- 114) Lobell, M. and Schneider, M. *Synthesis* **1994**, 375-377.
- 115) Doucet, H.; Martin-Vaca, B.; Bruneau, C. and Dixneuf, P. H. *J. Org. Chem.* **1995**, *60*, 7247-7255.
- 116) a) Wirz, B. and Spurr, P. *Tetrahedron Asymmetry* **1995**, *6*, 669-670; b) Huang, F-C, Lee, L. F. H.; Mittal, R. S. D.; Ravikumar, P. R.; Chan, J. A. and Sih, C. J. *J. Am. Chem. Soc.* **1975**, 4144-4145; c) Chen, C-S.; Fujimoto, Y. and Sih, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 3580-3582.
- 117) Gu, Q-M.; Chen, C-S. and Sih, C. J. *Tetrahedron Lett.* **1986**, *27*, 1763-1766.
- 118) Ahmar, M.; Girard, C. and Block, R. *Tetrahedron Lett.* **1989**, *30*, 7053-7056.
- 119) Prashad, M.; Har, D.; Repic, O.; Blacklock, T. J. and Giannousis, P. *Tetrahedron: Asymmetry* **1998**, *9*, 2133-2136.
- 120) Internet: info@altus.com, Homepage: www.altus.com.
- 121) Sobolov, S. B.; Bartoszko-Malik, A.; Oeschger, T. R. and Montalbano, M. M. *Tetrahedron Lett.* **1994**, *35*, 7751-7754.
- 122) a) St. Clair, N. L. and Navia, M. A. *J. Am. Chem. Soc.* **1992**, *114*, 7314-7316; b) Sobolov, S. B.; Leonida, M. D.; Bartoszko-Malik, A.; Voivodov, K. I.; McKinney, F.; Kim, J. and Fry, A. J. *J. Org. Chem.* **1996**, *61*, 2125-2128; c) Sygusch, J. and Beaudry, D. *J. Biol. Chem.* **1984**, *259*, 10222-10227.
- 123) Lalonde, J. J.; Govardhan, C.; Khalaf, N.; Martinez, A. G.; Visuri, K. and Margolin, A. L. *J. Am. Chem. Soc.* **1995**, *117*, 6845-6852.
- 124) Otera, J. *Chem. Rev.* **1993**, *93*, 1449-1470.
- 125) Khalaf, N.; Govardhan, C. P.; Lalonde, J. J.; Persichetti, A.; Wang, Y-F. and Margolin, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 5494-5495.

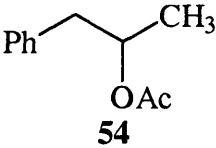
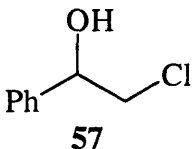
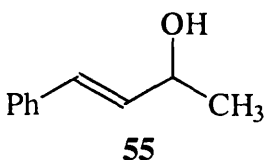
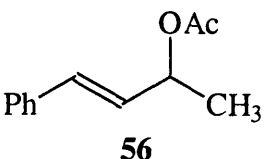
- 126) Persichetti, R. A.; Lalonde, J. J.; Govardhan, C. P.; Khalaf, N. K. and Margolin, A. L. *Tetrahedron Lett.* **1996**, 37, 6507-6510.
- 127) a) Rubio, E.; Fernandez-Mayorales, A. and Klibanov, A. M. *J. Am. Chem. Soc.* **1991**, 113, 695-696; b) Sakurai, T.; Margolin, A. L.; Russell, A. J. and Klibanov, A. M. *J. Am. Chem. Soc.* **1988**, 110, 7236-7237; c) Zaks, A. and Klibanov, A. M. *J. Am. Chem. Soc.* **1986**, 108, 2767-2768.
- 128) Kirchmer, G.; Scollar, M. P. and Klibanov, A. M. *J. Am. Chem. Soc.* **1985**, 107.
- 129) Stokes, T. M. and Oehlschager, A. C. *Tetrahedron Lett.* **1987**, 28, 2091-2094.
- 130) Chang, C-S.; Tsai, S-W. and Lin, C-N. *Tetrahedron: Asymmetry* **1998**, 9, 2799-2807.
- 131) Barton, D.; Laws, A. P. and Page, M. I. *J. Chem. Soc., Perkin Trans 2* **1994**, 2021-2029.
- 132) Vorde, C.; Högberg, H-E. and Hedenström, E. *Tetrahedron: Asymmetry* **1996**, 7, 1507-1513.
- 133) Cambou, B. and Klibanov, A. M. *J. Am. Chem. Soc.* **1984**, 106, 2687-2692.
- 134) Lloyd, R. C.; Dickman, M. and Jones, J. B. *Tetrahedron: Asymmetry* **1998**, 9, 551-561.
- 135) Fernholz, E.; Schloeder, D.; Liu, K. K-C.; Bradshaw, C. W.; Huang, H.; Janda, K.; Lerner, R. A. and Wong, C-W. *J. Org. Chem.* **1992**, 57, 4756-4761.
- 136) Li, R.; Powers, V. M.; Kozarich, J. W. and Kenyon, G. L. *J. Org. Chem.* **1995**, 60, 3347-3351.
- 137) Ebbers, E.; Ariaans, G. J. A.; Houbiers, J. P. M.; Bruggink, A. and Swanenburg, B. *Tetrahedron* **1997**, 53, 9417-9476.
- 138) Camps, P. and Gimenez, S. *Tetrahedron: Asymmetry* **1996**, 7, 1227-1234.

- 139) Liang, J.; Ruble, C. and Fu, G. C. *J. Org. Chem.* **1998**, *63*, 3154-3155.
- 140) Koh, K.; Ben, R. N. and Durst, T. *Tetrahedron Lett.* **1994**, *35*, 375-378.
- 141) Turner, N. J. and Winterman, J. *Tetrahedron Lett.* **1995**, *36*, 1113-1116.
- 142) Fülling, G. and Sih, C. J. *J. Am. Chem. Soc.* **1987**, *109*, 2845-2846.
- 143) Parmar, V. S.; Singh, A.; Bisht, K. S.; Kumar, N.; Belokon, Y. N.; Kochetkov, K. A.; Ikonnikov, N. S.; Orlova, S. A. and Saveleva, T. F. *J. Org. Chem.* **1996**, *61*, 1223-1227.
- 144) Um, P.-J. and Drueckhammer, D. G. *J. Am. Chem. Soc.* **1998**, *120*, 5605-5610.
- 145) The racemisation of (S)-**97** by BEMP-P in cyclohexane gave 27% ee and in ether gave 7.5% ee after 72 hours at room temperature. Acid (S)-**92** did not racemise under the above conditions. Phenyl ester (S)-**97** was mildly racemised by Et<sub>3</sub>N (1 eq) to give 67% ee after 43 hours at 40 °C in water/MeCN (10:1) and with Et<sub>3</sub>N (0.5 eq) phenyl ester (S)-**97** was recovered in 84% ee under the same reaction conditions.
- 146) Dinh, P. M. and Williams, J. M. J. *Tetrahedron Lett.* **1999**, *40*, 749-752.

## **Appendix A**

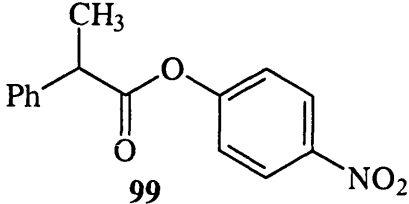
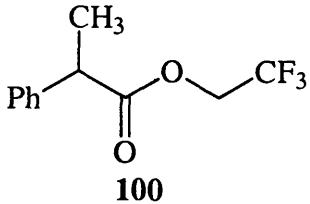
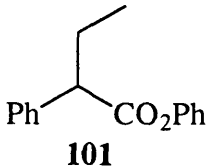
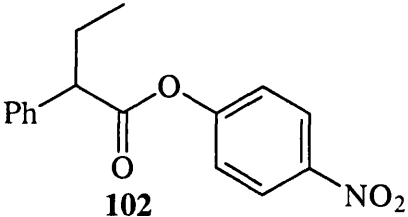
## HPLC Conditions

 <p>25</p>	<p>Column</p> <p>Mobile Phase</p> <p>Flow Rate</p> <p>Retention Time A</p> <p>Retention Time B</p>	<p>ChiralCel OD</p> <p>99:1 (Hex/IPA)</p> <p>1 mL/min</p> <p>18 min (R)-</p> <p>24 min (S)-</p>
 <p>26</p>	<p>Column</p> <p>Mobile Phase</p> <p>Flow Rate</p> <p>Retention Time A</p> <p>Retention Time B</p>	<p>ChiralCel OD</p> <p>99:1 (Hex/IPA)</p> <p>1 mL/min</p> <p>5.1 min (R)-</p> <p>5.5 min (S)-</p>
 <p>58</p>	<p>Column</p> <p>Mobile Phase</p> <p>Flow Rate</p> <p>Retention Time A</p> <p>Retention Time B</p>	<p>ChiralCel OD</p> <p>100 % Hexane</p> <p>1 mL/min</p> <p>7.5 min</p> <p>8.1 min</p>
 <p>53</p>	<p>Column</p> <p>Mobile Phase</p> <p>Flow Rate</p> <p>Retention Time A</p> <p>Retention Time B</p>	<p>ChiralCel OD</p> <p>99:1 (Hex/IPA)</p> <p>1 mL/min</p> <p>12.7 min (S)-</p> <p>15.0 min (R)-</p>

 <p><b>54</b></p>	<p>Column</p> <p>Mobile Phase</p> <p>Flow Rate</p> <p>Retention Time A</p> <p>Retention Time B</p>	<p>ChiralCel OD</p> <p>99:1 (Hex/IPA)</p> <p>1 mL/min</p> <p>5.0 min (S)-</p> <p>6.7 min (R)-</p>
 <p><b>57</b></p>	<p>Column</p> <p>Mobile Phase</p> <p>Flow Rate</p> <p>Retention Time A</p> <p>Retention Time B</p>	<p>ChiralCel OD</p> <p>98:2 (Hex/IPA)</p> <p>1 mL/min</p> <p>15.5 min (S)-</p> <p>18.6 min (R)-</p>
 <p><b>55</b></p>	<p>Column</p> <p>Mobile Phase</p> <p>Flow Rate</p> <p>Retention Time A</p> <p>Retention Time B</p>	<p>ChiralCel OJ</p> <p>99:1 (Hex/IPA)</p> <p>1 mL/min</p> <p>34.5 min</p> <p>37.7 min</p>
 <p><b>56</b></p>	<p>Column</p> <p>Mobile Phase</p> <p>Flow Rate</p> <p>Retention Time A</p> <p>Retention Time B</p>	<p>ChiralCel OJ</p> <p>99:1 (Hex/IPA)</p> <p>1 mL/min</p> <p>15.0 min</p> <p>20.4 min</p>



$  \begin{array}{c}  \text{CH}_3 \\    \\  \text{Ph}-\text{CH}-\text{CO}_2\text{H} \\  \mathbf{92}  \end{array}  $	<p>Column</p> <p>Mobile Phase</p> <p>Flow Rate</p> <p>Retention Time A</p> <p>Retention Time B</p>	<p>ChiralCel OD</p> <p>97.98:2:0.02 (Hex/IPA/HCO<sub>2</sub>H)</p> <p>1 mL/min</p> <p>13.4 min (R)-</p> <p>15.7 min (S)-</p>
$  \begin{array}{c}  \text{CH}_3 \\    \\  \text{Ph}-\text{CH}-\text{CO}_2\text{CH}_3 \\  \mathbf{96}  \end{array}  $	<p>Column</p> <p>Mobile Phase</p> <p>Flow Rate</p> <p>Retention Time A</p> <p>Retention Time B</p>	<p>ChiralCel OJ</p> <p>90:10 (Hex/IPA)</p> <p>1 mL/min</p> <p>7.5 min (R)-</p> <p>8.6 min (S)-</p>
$  \begin{array}{c}  \text{CH}_3 \\    \\  \text{Ph}-\text{CH}-\text{CO}_2\text{Ph} \\  \mathbf{97}  \end{array}  $	<p>Column</p> <p>Mobile Phase</p> <p>Flow Rate</p> <p>Retention Time A</p> <p>Retention Time B</p>	<p>ChiralPak AD</p> <p>98:2 (Hex/IPA)</p> <p>1 mL/min</p> <p>6.7 min (S)-</p> <p>8.5 min (R)-</p>
$  \begin{array}{c}  \text{CH}_3 \\    \\  \text{Ph}-\text{CH}-\text{CO}_2\text{CH}=\text{CH}_2 \\  \mathbf{98}  \end{array}  $	<p>Column</p> <p>Mobile Phase</p> <p>Flow Rate</p> <p>Retention Time A</p> <p>Retention Time B</p>	<p>ChiralCel OJ</p> <p>90:10 (Hex/IPA)</p> <p>1 mL/min</p> <p>6.2 min (S)-</p> <p>8.0 min (R)-</p>

 <p style="text-align: center;"><b>99</b></p>	<p>Column</p> <p>Mobile Phase</p> <p>Flow Rate</p> <p>Retention Time A</p> <p>Retention Time B</p>	<p>ChiralPak AD</p> <p>90:10 (Hex/IPA)</p> <p>1 mL/min</p> <p>9.8 min (S)-</p> <p>12.0 min (R)-</p>
 <p style="text-align: center;"><b>100</b></p>	<p>Column</p> <p>Mobile Phase</p> <p>Flow Rate</p> <p>Retention Time A</p> <p>Retention Time B</p>	<p>ChiralCel OJ</p> <p>90:10 (Hex/IPA)</p> <p>1 mL/min</p> <p>5.9 min (S)-</p> <p>6.5 min (R)-</p>
 <p style="text-align: center;"><b>101</b></p>	<p>Column</p> <p>Mobile Phase</p> <p>Flow Rate</p> <p>Retention Time A</p> <p>Retention Time B</p>	<p>ChiralPak AD</p> <p>97:3 (Hex/IPA)</p> <p>1 mL/min</p> <p>11.9 min</p> <p>14.3 min</p>
 <p style="text-align: center;"><b>102</b></p>	<p>Column</p> <p>Mobile Phase</p> <p>Flow Rate</p> <p>Retention Time A</p> <p>Retention Time B</p>	<p>ChiralCel OD</p> <p>97.98:2:0.02 (Hex/IPA/HCO<sub>2</sub>H)</p> <p>1 mL/min</p> <p>9.9 min</p> <p>11.57 min</p>